CONTENTS

The American Journal of Medicine

VOL. IX DECEMBER, 1950 NO. 6

Editorial

Clinical Studies

These instructive papers analyze the use of the ballistocardiogram in obtaining a rough approximation of the cardiac output but more particularly as an aid in detecting and assaying impaired myocardial function, angina pectoris, congenital cardiovascular anomalies and degenerative cardiovascular disease. The effect of respiration on the ballistocardiogram is subjected to special analysis.

Hypertension associated with coarctation of the aorta cannot be attributed solely to the mechanical effects of the constricting aortic lesion. However, studies of renal dynamics before and after surgery failed to show changes correlating with the blood pressure; hence the authors conclude that renal ischemia is not the additional causative factor in hypertension.

The absolute polycythemias (primary and secondary) could be distinguished from relative polycythemia by blood volume determinations using P^{32} labeled red blood cells. Inferences as to total red cell volume drawn from the hematocrit were found subject to error due to variations in plasma volume.

Contents continued on page 5

NEW

AMES DIAGNOSTIC REAGENT TABLET

BUMINTEST

for detection of albumin in urine

For office, laboratory or bedside determination of clinically significant albuminuria, *Bumintest* (Brand) Reagent Tablets have these advantages:

test is quick • noncaustic-noncorrosive

no heat required • inexpensive

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A modification of the well-established sulfosalicylic acid method, the amount of albumin present is estimated by the degree of turbidity.

For the rapid and more convenient performance of basic diagnostic tests without heating or special equipment, *Bumintest* (Brand) Reagent Tablets now join

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The American Journal of Medicine

VOL. IX DECEMBER, 1950 NO. 6

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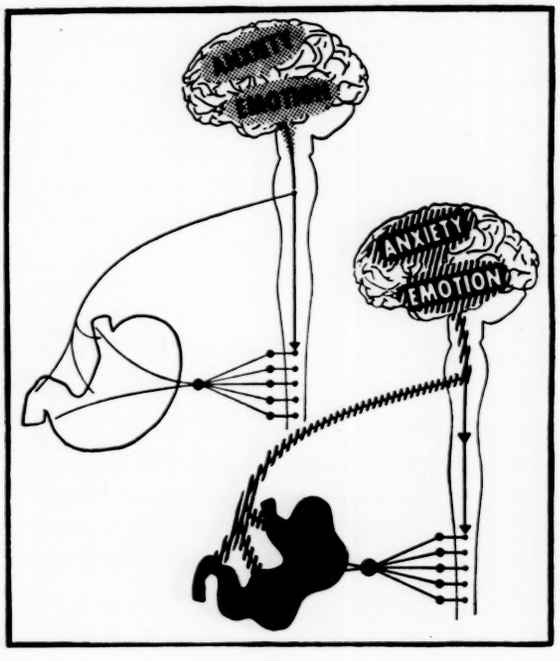
Contents continued on page 7

". . . about 50% of the patients who consult the general practitioner have complaints for which there is no discoverable physical or organic cause."[1]

Emotional response and adaptation to stress of the times play major roles in the increase of functional disorders. Exaggerated emotional response may produce somatic symptoms such as vague pains referred to various organs. Nausea, headache, cardiac and gastrointestinal distress are often presenting complaints. Diagnosis is usually easy in these cases because the number and variety of symptoms are not corroborated by physical findings. *Yet, these patients are seriously ill and merit attention and relief. Recent research has indicated that functional disturbances may develop into organic disease if long continued*[2]. In functional disorders, response to stress is effected via both branches of the autonomic nervous system. Therefore, treatment consists, where possible, in removal of the emotogenic factor (practical psychotherapy) and the "partial blockade" of the efferent autonomic pathways.

The family physician is well qualified to help these patients since he is most often aware of the environmental circumstances. His advice and guidance will do much to achieve the desired change in activities and habits and will help the patient to avoid "unhealthy situations".



Medical treatment is also essential in most cases. Controlled sedation of the entire autonomic nervous system accelerates recovery. This is accomplished by simultaneous administration of Bellafoline (cholinergic inhibitor), ergotamine tartrate (adrenergic inhibitor) and phenobarbital (central sedative).

Bellergal is a time tested preparation for administration in a wide variety of functional disorders. Bellergal inhibits the transmission of autonomic impulses without completely blocking organ function. This type of "mild sedation" will permit the patient to carry on daily activities while "taking stock of his difficulties". Karnosh and Zucker[3] state that, "Probably the best medication for all neurovegetative disorders is a combination of: (a) Bellafoline... (b) Ergotamine tartrate... (c) Phenobarbital... A good commercial preparation of these ingredients is a tablet called bellergal... The adult dose of bellergal is 3 or 4 tablets daily."

BIBLIOGRAPHY

1. WILLIAMS, V. P.: Medical Progress: Psychiatry, New England J. Med. *236:* 322-326 (Feb. 27) 1947.
2. NAIA, J. A.: Psyche and Somatic Disorders, Neurobiologia *9:* 269-278, 1946: Psychosom. Med. *10:* 120 (March-April) 1948.
3. KARNOSH, L. J. and ZUCKER, E. N.: A Handbook of Psychiatry, St. Louis, The C. V. Mosby Company, 1945, p. 248.

Brochures available on request:
"The A.N.S. and Functional Disorders."
"The Menopause Needs More Than Hormones."
"The A.N.S. and—Gastrointestinal Disorders—Cardiac Neuroses —Gynecological Problems—Anxiety States." (A series)

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The American Journal of Medicine

VOL. IX DECEMBER, 1950 NO. 6

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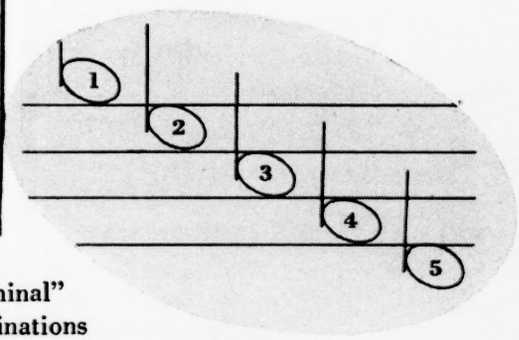
Clinico-pathologic Conference

Case Report

variations on a theme...



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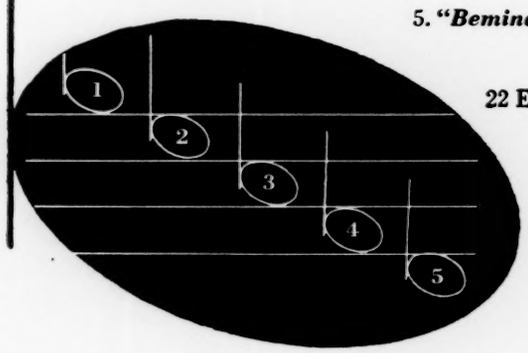

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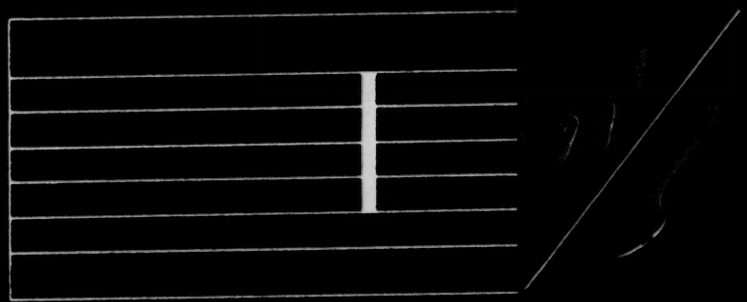

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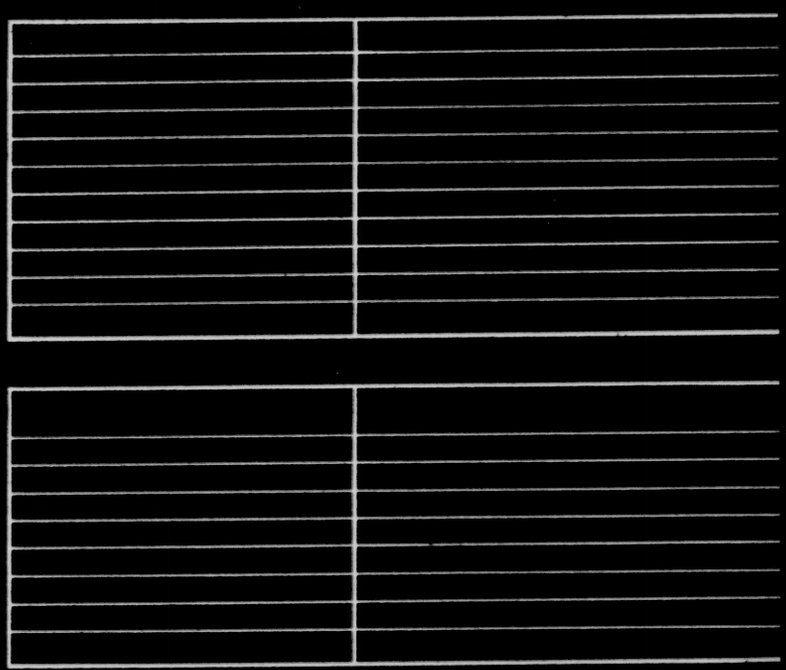
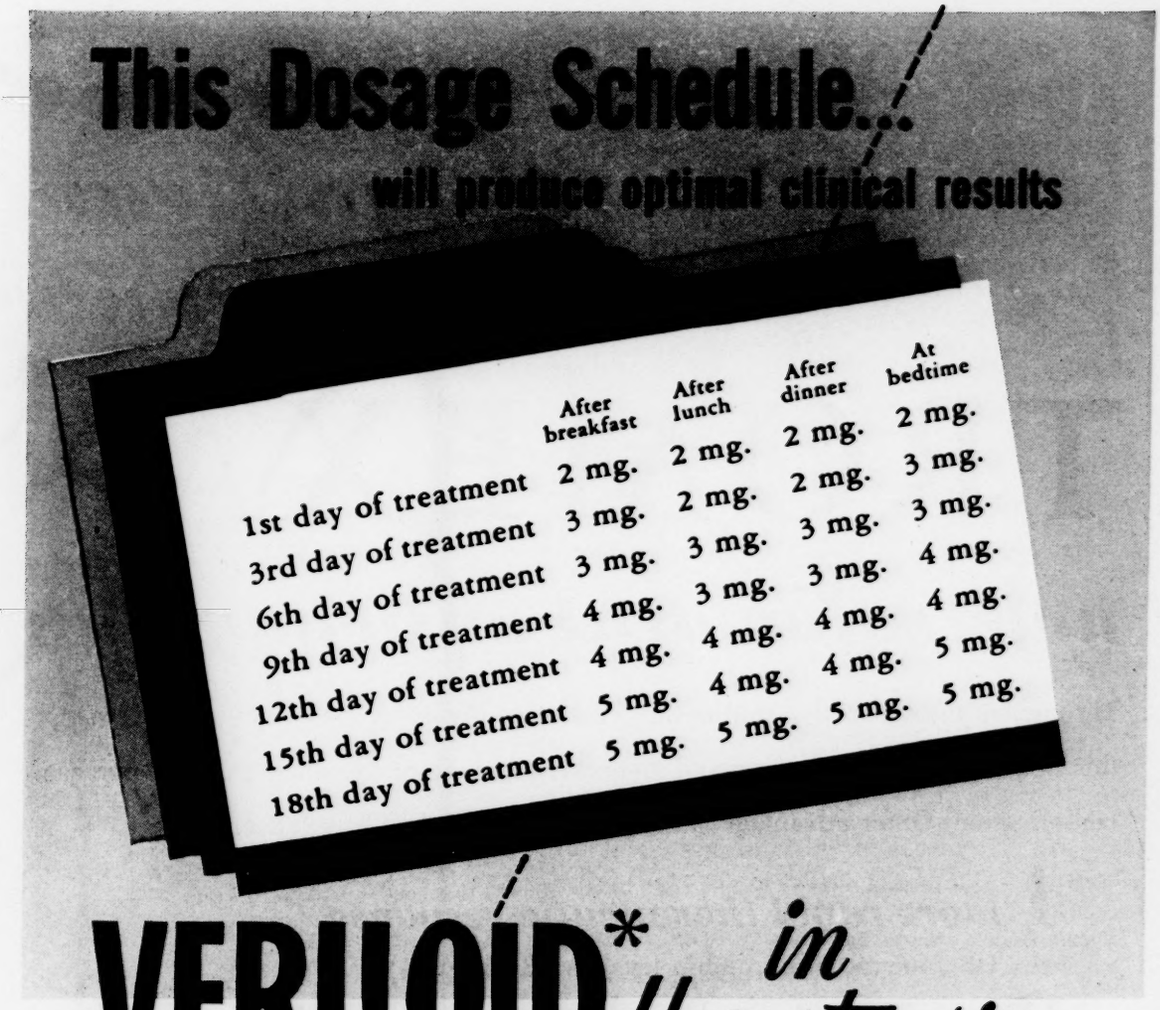


BOOK SECTION

"We have not read an author till we have seen his object, whatever it may be, as he saw it."

—Carlyle



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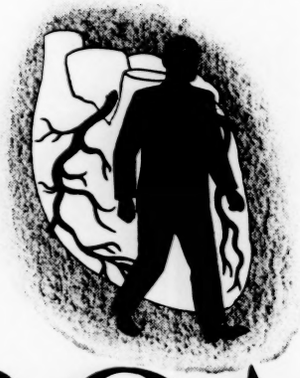

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new, safer, oral anticoagulant

Throughout the exhaustive studies on TROMEXAN, involving many hundreds of cases, this new anticoagulant has proved singularly free from the dangers of hemorrhagic complication. Other advantageous clinical features of TROMEXAN are:

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Now—with Chlorophyll . . .

A tissue-stimulating Chloresium Powder

Promotes healthy granulation tissue at the ulcer site—gives prompt, soothing symptomatic relief

A new and fundamental approach to the treatment of chronic and acute peptic ulcers is made possible by Chloresium Powder.

Perfected after three years of research by Rystan Company, originator of therapeutic water-soluble chlorophyll preparations, this combination product assures prolonged contact of *tissue-stimulating* chlorophyll with the ulcer crater.

Clinical evidence shows that it offers six distinct advantages:

1. Promotes healthy granulation tissue at the ulcer site.

2. Gives prompt symptomatic relief.

3. Provides a prolonged protective coating.

4. Provides prompt antacid action—no alkalosis, no acid rebound, no interference with bowel regularity.

5. Completely safe, absolutely nontoxic.

6. Minimizes—often eliminates—need for special diets and restricted activity.

How it works

A three-way combination product, Chloresium Powder provides the antacid and protective actions of the usual peptic ulcer preparations with aluminum hydroxide and magnesium trisilicate in a specially prepared dehydrated okra base. *The addition of the water-soluble derivatives of chlorophyll "a" gives you a healing therapy that actually promotes healthy granulation tissue at the ulcer site.*

"The high incidence of patients who have gone through one ulcer regimen after another with temporary relief, but with no healing of the ulcer crater, suggests the need of supplying direct assistance to the damaged gastroduodenal[1] tissues in the form of a tissue-stimulant."

Chloresium Powder provides prolonged contact of tissue-stimulating chlorophyll *with the ulcer crater.*

therapy for peptic ulcers!

Dramatic results in long-standing peptic ulcer cases

In a recently reported clinical series[1], complete healing was obtained in 58 out of 79 cases of *long-standing* peptic ulcers within 2 to 7 weeks—with this new chlorophyll powder!

Chloresium Powder, in this clinical trial, demonstrated its effectiveness to the peptic ulcer patient quickly in the form of complete symptomatic relief. It demonstrated its effectiveness to the physician, under roentgenological examination, in prompt healing of the ulcer crater—usually in 2 to 7 weeks—even in cases which had been resistant to other therapy.

The minimum known history of the cases treated was two years. Many of the ulcers healed had resisted previous methods of treatment for from 5 to 12 years.

No special diets required

To avoid factors whose beneficial effects might be difficult to disassociate from the effects of the Chloresium Powder, no special diets were prescribed. There were no restrictions on smoking, alcoholic beverages or daily activity. Nevertheless, 3 out of 4 cases not only got lasting symptomatic relief in 1 to 3 days, but also obtained *complete healing of the ulcers* in 2 to 7 weeks.

These remarkable results—obtained with complete freedom from dietary and other restrictions—indicate that here at last is a therapy which can be administered without upsetting the patient's normal habits and can thus greatly simplify the task of insuring patient co-operation. Moreover, Chloresium Powder is palatable and easily taken by the patient.

1. Offenkrantz, W. F., *Rev. Gastroenterol*, 17:359-367 (May), 1950.

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Natural nontoxic chlorophyll therapy for the treatment of peptic ulcers.

Try it on your most difficult case —mail coupon today!

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"Reduces the postoperative hospital stay by 50%"

" '*Dexedrine*' *Sulfate*, administered orally after surgery of the eye, ear, nose and throat . . . results in earlier ambulation, shortens hospitalization and hastens postoperative recovery," according to a recently published paper.[1]

Reporting on a series of 220 patients (mostly children, who were given '*Dexedrine*' in the elixir dosage form), the author states:

1. "By mid-afternoon (only 6 or 7 hours after operation) patients were awake and active.
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Dexedrine* Sulfate tablets • elixir

the antidepressant of choice

1. *Barnett, S.E.: Eye, Ear, Nose & Throat Monthly 39:19, 1950.*

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team for oral therapy

The daily administration of one or two Tablets MERCUHYDRIN® with Ascorbic Acid usually produces adequate diuresis in the cardiac patient whose water and electrolyte balance *has already been stabilized by parenteral mercurial diuretic therapy*. At this stage, the edema-free state — manifested by the unfluctuating basic weight — can be maintained with the tablets, either alone or supplemented by injections at appropriate intervals.

Such a schedule now gives time-honored digitalis a worthy partner in the fight against the failing heart. Maintaining the cardiac patient free of signs and symptoms of failure is facilitated by dual oral therapy — MERCUHYDRIN Tablets with Ascorbic Acid teamed with oral digitalis preparations.

tablets

MERCUHYDRIN

with Ascorbic Acid

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The systematic use of MERCUHYDRIN Tablets with Ascorbic Acid simplifies treatment for patient and physician — injections are considerably reduced or eliminated, and visits to the physician's office are kept to a minimum.

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Tablets MERCUHYDRIN with Ascorbic Acid, available in bottles of 100 tablets. Each tablet contains meralluride 60 mg. (equivalent to 19.5 mg. mercury) and ascorbic acid 100 mg.

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Gratifying Relief

from distressing symptoms

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Pyridium is the trade-mark of Nepera Chemical Co., Inc., successor to Pyridium Corporation, for its brand of phenylazo-diamino-pyridine HCl. Merck & Co., Inc. sole distributor in the United States.

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For local treatment and prophylaxis of oral infections caused by penicillin-sensitive organisms.

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When your diagnosis is idiopathic hypochromic anemia with a poor nutritional history, IBEROL tablets offer effective, convenient therapy—just one tablet three times daily with meals.

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Riboflavin	6 mg. (3xMDR*)
Nicotinamide	30 mg. (2xRDA†)
Ascorbic Acid	150 mg. (5xMDR*)
Pyridoxine Hydrochloride	3 mg.
Pantothenic Acid	6 mg.
Vitamin B_{12}	6 mcg.
Folic Acid	3.6 mg.
Stomach-Liver Digest	1.5 Gm.

*MDR—Minimum Daily Requirement
†RDA—Recommended Daily Dietary Allowance

When more than iron is needed, see that the Rx reads

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(Iron, Vitamin B Complex, Stomach-Liver Digest, Abbott)

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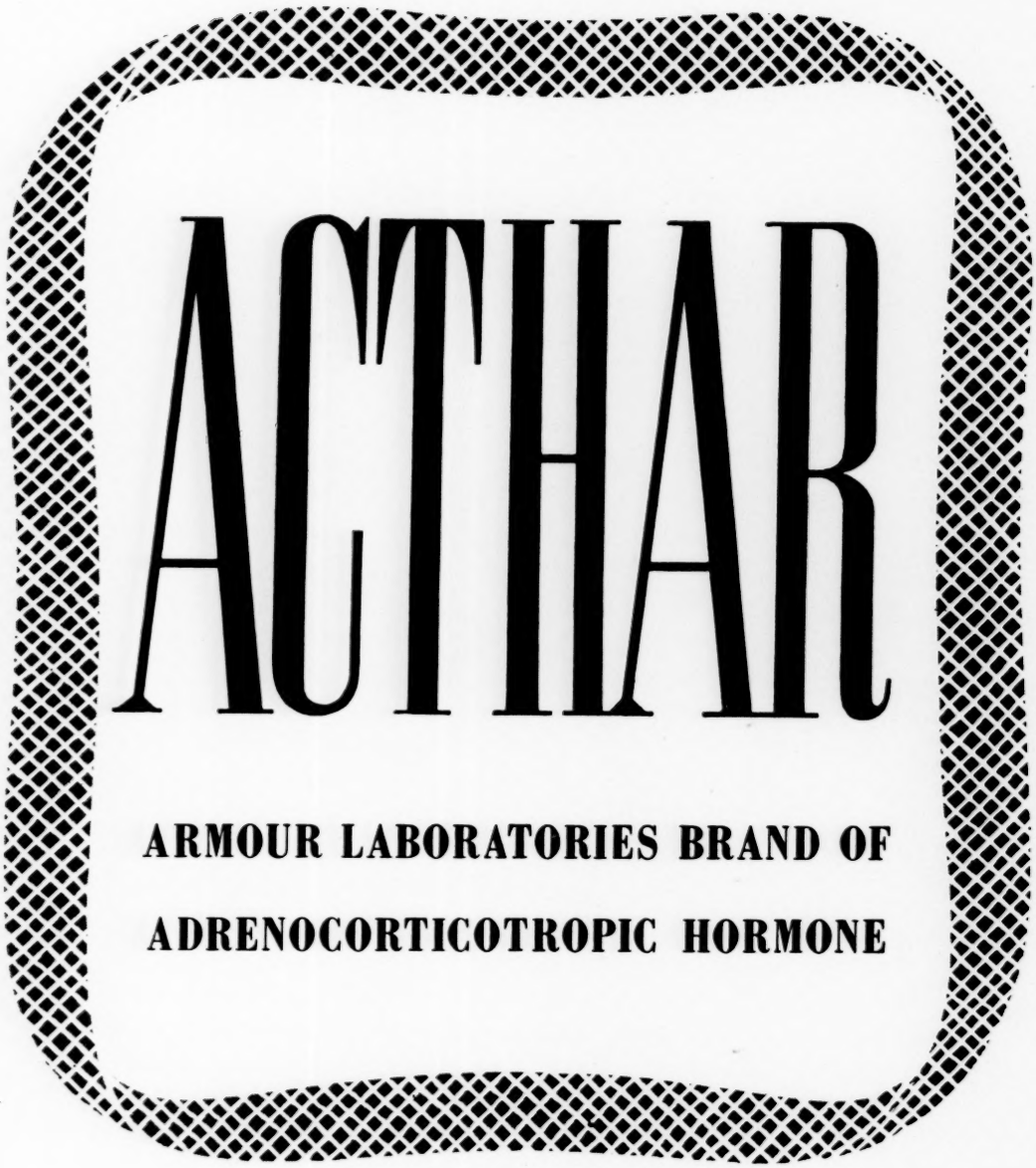

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High Vitamin B_{12} Content... Another Reason for Liberal Meat Intake

According to rapidly accumulating clinical and laboratory observations, the daily ingestion of liberal quantities of meat can effect profound physiologic benefits due to the significant content of vitamin B_{12}, not only in liver and kidney, but also in muscle meats.

Muscle meat is a good source of the newly isolated vitamin B_{12}; liver and kidney are especially high in their vitamin B_{12} content, while plant foods are negligible sources of this nutrient.[1] By rat assay, the minimum amounts of vitamin B_{12} in muscle meat range from 0.5 to 3 mcg. per 100 Gm.; minimum values for beef liver and kidney are 15 and 20 mcg., respectively.[2]

B_{12} is among the most potent of known microbiologically active substances.[3] Animal studies indicate that it increases the ability of the normal mammal to utilize protein.[4] With a high protein diet, 0.01 mcg. of vitamin B_{12} per day was found to increase significantly the growth rate of B_{12} deficient rats. In another study, growth response of B_{12} depleted rats was proportional to the B_{12} in the ration within the critical range of 0.025 to 0.1 mcg. per rat day.[5]

About 1 mcg. of vitamin B_{12} daily, administered intramuscularly, constitutes an effective dose in pernicious anemia. In a recent clinical study of young children manifesting vitamin B_{12} deficiency as evidenced by malnutrition and growth failure, oral administration of 10 mcg. of vitamin B_{12} daily for eight weeks induced marked responses in growth; notable increases in vigor, alertness and better general behavior; and improved appetite.[6]

Here again is further evidence of the broad, over-all nutrient contribution meat makes to the dietary. Eaten two or three times daily, it supplies not only generous amounts of high quality protein, but also significant quantities of vitamin B_{12} and other essential B complex vitamins, and of iron.

---

(1) Schweigert B. S.: Significance of Vitamin B_{12} and Related Factors, J. Am. Dietetic Assoc. *26*:782 (Oct.) 1950.

(2) Lewis, U. J.; Register, U. D.; Thompson, H. T., and Elvehjem, C. A.: Distribution of Vitamin B_{12} in Natural Materials, Proc. Soc. Exper. Biol. & Med. *72*:479 (Nov.) 1949.

(3) Shorb, M. S.: Activity of Vitamin B_{12} for the Growth of Lactobacillus lactis, Science *107*:397 (Apr. 16) 1948.

(4) Hartman, A. M.; Dryden, L. P., and Cary, C. A.: The Role and Sources of Vitamin B_{12}, J. Am. Dietetic Assoc. *25*:929 (Nov.) 1949.

(5) Frost, D. V.; Fricke, H. H., and Spruth, H. C.: Rat Growth Assay for Vitamin B_{12}, Proc. Soc. Exper. Biol. & Med. *72*:102 (Oct.) 1949.

(6) Wetzel, N. C.; Fargo, W. C.; Smith, I. H., and Helikson, J.: Growth Failure in School Children as Associated with Vitamin B_{12} Deficiency—Response to Oral Therapy, Science *110*:651 (Dec. 16) 1949.

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exercise in simple logic

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"Sulfacetimide appears the most advantageous for third place."[1]

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is more desirable and offers many advantages in sulfonamide therapy.

TRICOMBISUL: Tablets 0.5 Gm., each containing 0.166 Gm. sulfa*cetimide*, 0.166 Gm. sulfadiazine and 0.166 Gm. sulfamerazine. Available in bottles of 100 and 1000 tablets.

1. Lehr, D.: Scientific Exhibit, Atlantic City Session, American Medical Association, June 6-10, 1949.

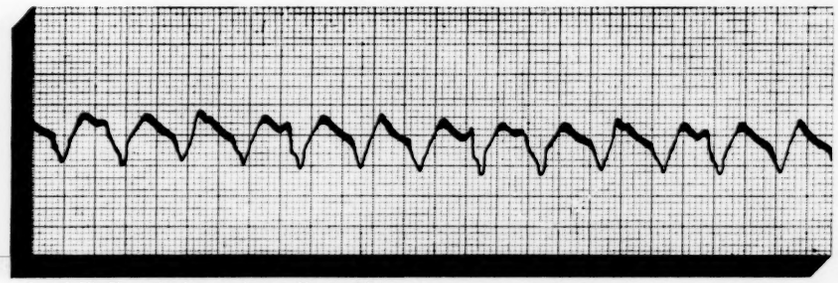
•T.M.

Schering CORPORATION

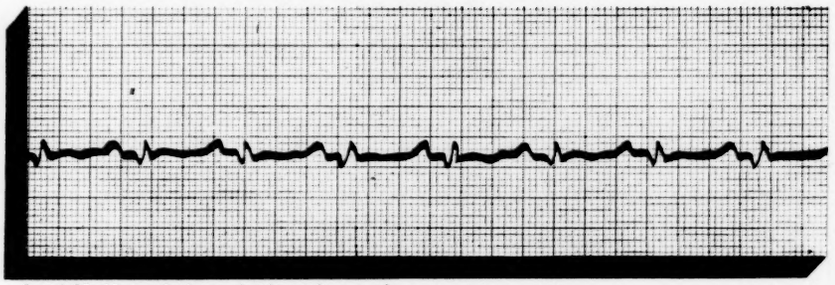
BLOOMFIELD, NEW JERSEY

TRICOMBISUL

A New Drug..for the treatment of ventricular arrhythmias



Lead II. Ventricular tachycardia persisting after six days of oral quinidine therapy (8 Gm. per day).



Lead II. Normal sinus rhythm after oral Pronestyl therapy.

Effective in some patients with ventricular tachycardia who failed to respond to quinidine

PRONESTYL *Hydrochloride*

Squibb Procaine Amide Hydrochloride

SQUIBB

new product brief

PRONESTYL *Hydrochloride*

Squibb Procaine Amide Hydrochloride

for the treatment of ventricular arrhythmias

What is it?

Pronestyl Hydrochloride is Squibb procaine amide hydrochloride. Structurally, Pronestyl differs from procaine only by the presence of the amide grouping (.CO.NH.) in Pronestyl where procaine has the ester grouping (.CO.O.)

How does it act?

The action of Pronestyl is probably due to a direct depressant action on the ventricular muscle. In auricular arrhythmias, preliminary observations indicate that Pronestyl slows auricular rate but usually does not re-establish normal sinus rhythm. At present, Pronestyl is not recommended in the treatment of auricular arrhythmias.

When is it indicated?

In conscious patients, for the treatment of ventricular arrhythmias.

During anesthesia, to correct cardiac arrhythmias.

What are its advantages in ventricular arrhythmias?

As compared with quinidine: Unlike quinidine, no important toxic symptoms have been reported following the use of Pronestyl orally. In therapeutic dosage, Pronestyl orally does not produce the nausea, vomiting, and diarrhea often caused by quinidine. At high oral dosage, these symptoms may appear.

Whereas intravenous administration of quinidine is hazardous and unpredictable, Pronestyl may be given intravenously with relative safety.

Pronestyl has been found effective in some patients who failed to respond to quinidine.

As compared with procaine: For arrhythmias, procaine is used only in anesthetized patients because its dose in unanesthetized patients is too toxic for clinical use. Pronestyl can be used in conscious and anesthetized patients.

Intravenously, Pronestyl is much less toxic than procaine. In the recommended intravenous dosage, Pronestyl does not cause the central nervous system stimulation typical of procaine in conscious patients.

Procaine is unstable, being rapidly hydrolyzed in the plasma to para-aminobenzoic acid and diethylaminoethanol. Pronestyl is not affected by the plasma procaine esterase, consequently it is much longer acting than procaine.

Procaine is not used orally because of its instability in the organism; Pronestyl can be used orally and intravenously.

What are its side effects?

Oral administration of Pronestyl in doses of 3-6 grams per day, for periods of time varying from 2 days to 3 months, produced no toxic effects as evidenced by studies of the blood count, urine, liver function, blood pressure, and electrocardiogram. Intravenous administration to patients without ventricular tachycardia produced only a moderate and transient hypotensive effect in about one-third of the subjects. However, during intravenous administration to patients with ventricular tachycardia, a striking hypotensive effect was almost invariably present. This disappeared concurrently with the establishment of a normal rhythm. Further studies are in progress to see whether the drug may be given intravenously over a period of time longer than five minutes so as to revert the ventricular tachycardia without causing hypotension. That this may be possible is indicated by the fact that some episodes of ventricular tachycardia have been successfully treated by oral administration without significant change in blood pressure. Electrocardiographic changes: prolongation of QRS and QT intervals and occasional diminution in voltage of QRS and T waves have occurred.

What is the dosage?

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ORALLY: 1 Gm. followed by 0.5-1.0 Gm. every four to six hours as indicated.

INTRAVENOUSLY: 200-1000 mg. (2 to 10 cc. Pronestyl Hydrochloride Solution). *Caution—administer no more than 200 mg. (2 cc.) per minute.*

Hypotension may occur during intravenous use in conscious patients. As a precautionary measure, administer at a rate no greater than 200 mg. (2 cc.) per minute to a total of no more than 1 Gm. Electrocardiographic tracings should be made during injection so that injection may be discontinued when tachycardia is interrupted. Blood pressure recordings should be made frequently during injection. If marked hypotension occurs, rate of injection should be slowed or stopped.

For the treatment of runs of ventricular extrasystoles:

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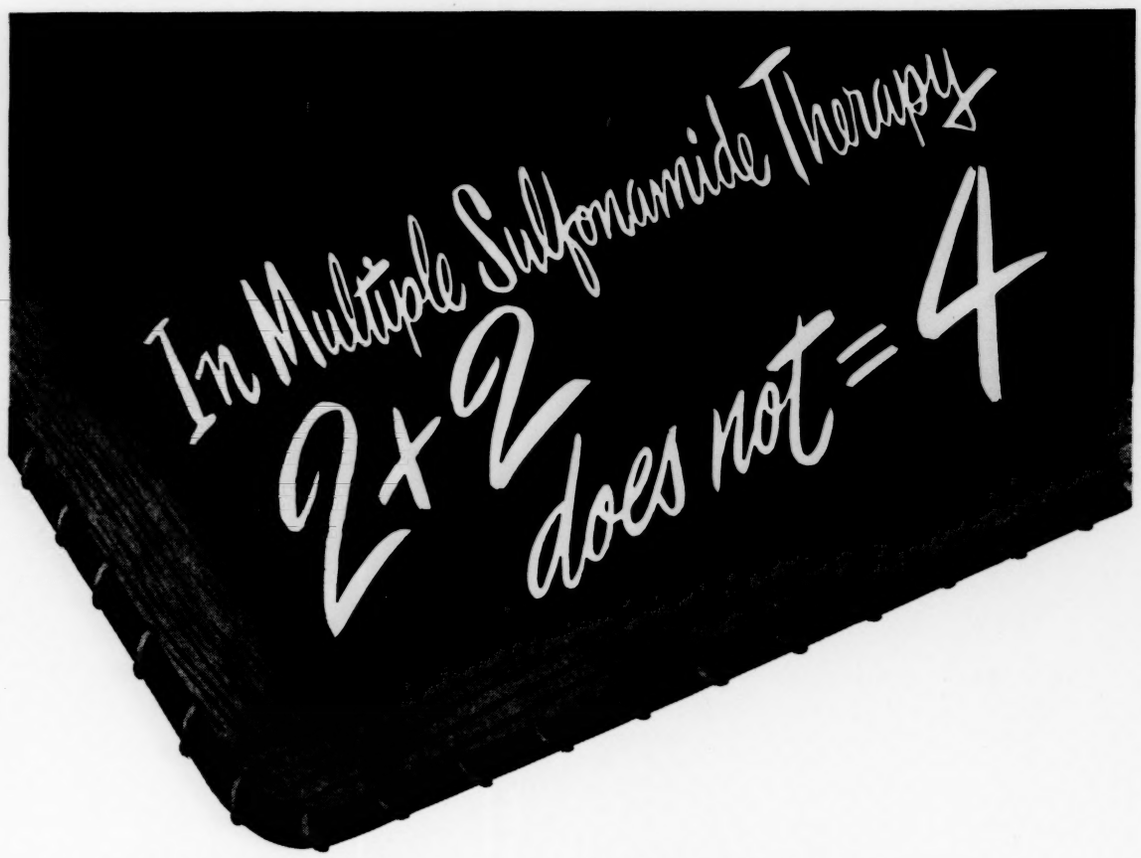

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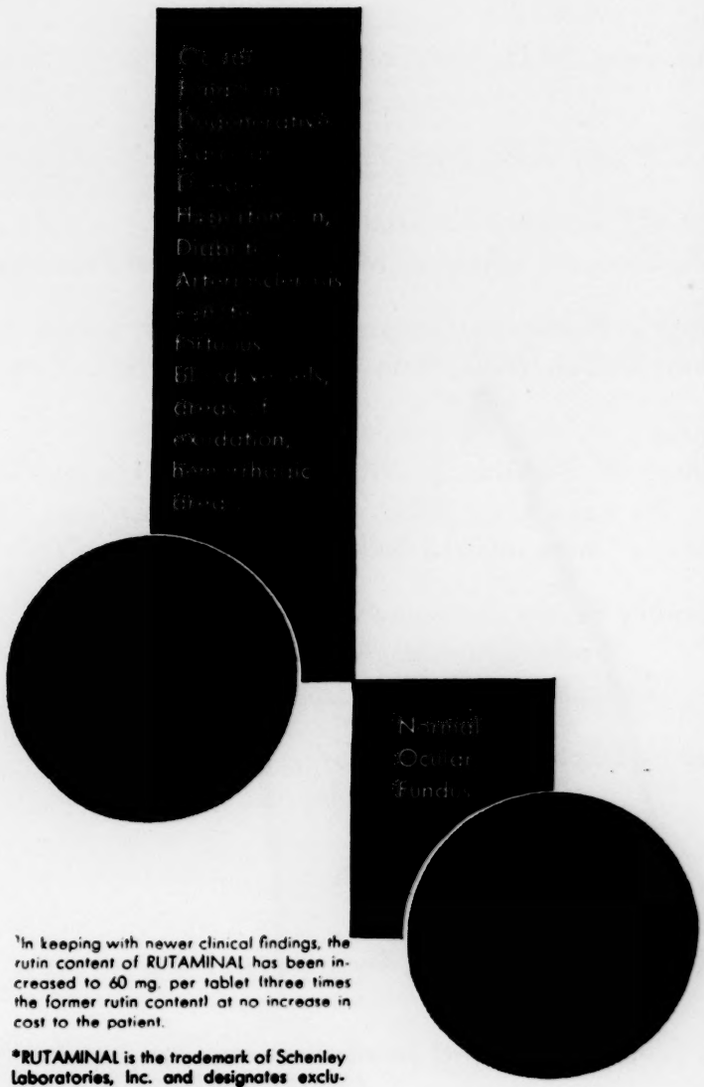

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1. Blake, F. G.; Friou, G. J., and Wagner, R. R.: Yale J. Biol. and Med. 22:495 (July) 1950.

2. Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950.

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Editorial

ACTH and Cortisone in Hemopoietic Disorders

With the synthesis of 11-dehydro-17-hydroxycorticosterone (Compound E (Kendall), Cortisone) and the production of the comparatively pure adrenocorticotrophic hormone (ACTH) from the pituitary in relatively large amounts, it is natural that therapeutic trials should be made in conditions characterized by lymphoid hyperplasia and in disorders of the hemopoietic system. The ground for such studies was laid by the investigations of Dougherty and White[1] who showed that increased adrenal cortical activity results in involution of normal lymphoid tissues. Subsequently Heilman and Kendall[2] reported that the administration of Compound E caused regression of a lymphoid tumor in mice.

The introduction of these substances as therapeutic agents was met with a burst of enthusiasm and hope which now appear to have been greater than justified. Even though all the observations presented so far are of a preliminary character, there is reason to believe that benefit is temporary and can be expected only in a limited number of cases. At the same time, however, channels of thought and of investigation have been opened up which should lead to worth while results.

Pearson and his associates[3] gave ACTH to three patients with chronic lymphatic leukemia, and one each with follicular lymphoblastoma, Hodgkin's disease, carcinoma of the prostate and metastatic carcinoma of the breast. One patient with chronic lymphatic leukemia was given cortisone acetate. In the six patients with lymphomatous tumors there was a dramatic and progressive decrease in the size of the enlarged lymph nodes and of enlarged spleens and this was accompanied by an increasing sense of well being and improved appetite. The leukocyte counts rose, nevertheless, in the cases of leukemia from levels of 250,000 to 500,000 per c.mm. to levels of 500,000 to 1,250,000. No significant alteration in hemoglobin levels took place. After therapy was discontinued, however, the leukocyte counts fell below the initial levels and in some cases there was no evidence of regrowth of lymphoid tissues ten weeks later. Somewhat similar slight to moderate and temporary benefit in three cases of chronic lymphocytic leukemia and in three cases of Hodgkin's disease has been described by Stickney, Heck and Watkins.[4]

[1] DOUGHERTY, T. F. and WHITE, A. Effect of pituitary adrenotropic hormone on lymphoid tissue *Proc. Soc. Exper. Biol. & Med.*, 53: 132, 1943.

[2] HEILMAN, F. R. and KENDALL, E. C. The influence of 11-dehydro-17-hydroxycorticosterone (compound E) on the growth of a malignant tumor in the mouse. *Endocrinology*, 34: 416, 1944.

[3] PEARSON, O. H., ELIEL, L. P., RAWSON, R. W., DOBRINER, K. and RHOADS, C. P. ACTH- and cortisone-induced regression of lymphoid tumors in man. *Cancer*, 2: 943, 1949.

[4] STICKNEY, J. M., HECK, F. J. and WATKINS, C. H. The effect of cortisone and ACTH on diseases of the blood. Blood Club Symposium, Atlantic City, N. J., April 30, 1950.

In some cases of acute leukemia more impressive though temporary changes have been observed. Farber[5] recently reported substantial remissions in five of seventeen patients treated with ACTH, with some benefit in an additional five of this group. Burchenal, Pearson and their associates[6] described good clinical and hematologic remissions in thirteen of thirty cases and some improvement in an additional nine; however, of these twenty-two cases in which improvement had been observed, twelve were already dead. Dameshek amplified on a published report[7] in which complete and incomplete remissions were described in five of eight patients. Wintrobe and associates[8] presented data in eight cases. Dramatic benefit was observed in a young woman treated with ACTH and varying degrees of improvement took place in four other cases, whereas there was total failure in three. When benefit occurred fever disappeared, appetite improved and sometimes became ravenous, adenopathy and splenomegaly were reduced, abnormal cells disappeared from the blood and became scarce in the bone marrow, and the red cell counts and platelets rose to normal. Remissions, however, varied in degree and were temporary.

Thus the administration of ACTH in acute leukemia was associated with slight to marked improvement in as many as 60 to 70 per cent of the patients treated but really substantial benefit has been much less frequent and cases of dramatic improvement appear to have been the exception. The effects of cortisone have been similar. It is noteworthy that improvement has been observed both in adults and in children although, as in the case of the folic acid antagonists, it has been seen more often in the latter than in the former. There is no clear evidence as yet that more striking effects may take place in lymphoblastic than in myeloblastic types. There have been several failures in cases of acute monocytic leukemia.[6,8]

Studying the effects of ACTH in other types of hemopoietic disorders, such as pernicious anemia, aplastic anemia, purpura hemorrhagica, myelophthisic anemia, multiple myeloma and anemia associated with rheumatoid arthritis, acute and chronic nephritis, cirrhosis and disseminated lupus erythematosus, Wintrobe et al.[8] noted stimulation of the granulopoietic tissue as manifested by the development of neutrophilic leukocytosis in thirteen of sixteen cases, a distinct though irregular reticulocytosis in eight cases, the appearance of nucleated red cells in the circulating blood in one case and a rise in the platelet count in several. No clinical improvement took place in these cases, however, except in the cases of lupus, arthritis and purpura. In the case of purpura hemorrhagica, the bleeding time and the clot retraction returned temporarily to normal as the platelet count rose.

While in none of these studies was there evidence of permanent beneficial effects or perhaps even of really valuable temporary improvement which could not be achieved by other means, the interesting fact remains that ACTH and cortisone can influence the hemopoietic system to a significant degree and in this sense a new era of research in hematology may be anticipated. That the hormones influence the blood-forming tissues has long been suspected and animal experiments have been reported from time to time which have indicated a relationship of the sex hormones and thyroxin, as well as of products of the pituitary-adrenal system, to the blood-forming tissues.[9] The changes

[5] FARBER, S. Blood Club Symposium, Atlantic City, N. J., April 30, 1950.

[6] PEARSON, O. H., ELIEL, L. P., TALBOT, T. R., JR., BURCHENAL, J. R., PETRO, A. T., POPPELL, J. W. and CRAVER, L. F. The use of ACTH and cortisone in acute leukemia. Blood Club Symposium, Atlantic City, N. J., April 30, 1950.

[7] DAMESHEK, W., SAUNDERS, R. H., JR. and ZANNOS, L. The use of ACTH in the treatment of acute and subacute leukemia. *Bull. New England M. Center*, 12: 11, 1950.

[8] WINTROBE, M. M., CARTWRIGHT, G. E., KUHNS, W. J., PALMER, J. G. and LAHEY, M. E. The effects of ACTH on the hematopoietic system. Blood Club Symposium, Atlantic City, N. J., April 30, 1950.

[9] GORDON, A. S. and CHARIPPER, H. A. The endocrine system and hemopoiesis. *Ann. New York Acad. Sc.*, 48: 615, 1947.

which have been described, however, have been of small degree and have not evoked wide interest. Nevertheless, if the hormones exert a controlling influence on the hemopoietic system, as seems quite possible, it must be borne in mind that their effects are likely to be of small magnitude as compared with those produced by the administration of substances like liver extract or iron when anemia is due to their specific deficiencies. Exceptionally painstaking observations will therefore have to be made.

Returning to the clinical effects of ACTH and cortisone, it should be pointed out that, in the quantities used in the studies described above, effects have been induced which are undesirable and may be dangerous. Fluid retention and edema occur commonly and symptoms of Cushing's syndrome may develop in various degrees: "moon face," hypertension, acne and hirsutism. The hypokalemic alkalosis described by Kepler et al.[10] in Cushing's syndrome may develop with low serum chloride and potassium levels and high serum pH and bicarbonate. The serum potassium may fall to dangerous levels and electrocardiographic changes characteristic of potassium deficit have been observed.[3] Although good therapeutic results have been obtained in some cases without the development of clinically significant symptoms or signs of hypercorticism, it must be borne in mind that to achieve therapeutic benefit doses have had to be used which are in excess of the endogenous production of these hormones. It may be added that there has been no correlation between magnitude of dosage and either therapeutic effect or occurrence of evidence of excess adrenal cortical stimulation.

The mode of action of the hormones on the hemopoietic system is quite obscure. There is considerable evidence, however, that the cortical hormones, like other endocrine secretions, probably exert a potentiating and regulating effect, accelerating or controlling metabolic processes which may proceed even in the absence of the hormones. They influence many body processes but are not essential for them. This has, in fact, been demonstrated in relation to the disturbance in iron metabolism which accompanies the anemia of infection.[11]

If this concept is correct, it should be expected that except where hormone administration meets a deficiency, as in hypothyroidism and in Addison's disease, one should observe only temporary benefits from their use. At least in relation to the hemopoietic disorders, inconsistency in clinical response, depending on the nature and severity of the underlying process, and escape from the effects achieved, would be expected.

MAXWELL M. WINTROBE, M.D.

[10] WILLSON, D. M., POWER, M. H. and KEPLER, E. J. Alkalosis and low plasma potassium in a case of Cushing's syndrome: a metabolic study. *J. Clin. Investigation*, 19: 701, 1940.

[11] CARTWRIGHT, G. E., HAMILTON, L. D., GUBLER, C. J., KUHNS, W. J. and FELLOWS, N. M. The role of the reticulo-endothelial system and the adrenal cortex in the regulation of the plasma iron level. Am. Soc. Clin. Invest., Atlantic City, N. J., May 1, 1950.

Clinical Studies

Ballistocardiogram, Description and Clinical Use*

HERBERT R. BROWN, JR., M.D. *and* VINCENT DE LALLA, JR., M.D.
Rochester, New York *Utica, New York*

GORDON[1] first demonstrated in 1877 that the motions imparted to the body by the "mechanical heart action" could be recorded; since then numerous observers have reported their observations on and methods of recording what has come to be known as the ballistocardiogram. Yandell Henderson in 1905 further developed the apparatus described by Gordon and changed it to a horizontal table which was suspended from the ceiling by four wires. The recoil motions imparted to it were recorded by mechanical amplification.[2] In 1922 Heald and Tucker recorded the recoil movements of the body by means of a vertical apparatus and an ingenious hot wire microphone.[3] Starr gave the greatest impetus to this instrument when he demonstrated the value of the ballistocardiograph as an instrument for measuring relative cardiac output and, more important, as an instrument with real diagnostic significance.[4–8]

CHARACTERISTICS OF THE NORMAL BALLISTOCARDIOGRAM

The tracings shown were taken on a high frequency table and in the manner described by Brown and Pearson;[9] upward deflections are caused by headward forces, downward deflections are caused by footward forces.

There are four channels in nearly all of the figures presented, namely, (1) respiration: top undulating line (inspiration represented by a downward deflection and expiration by an upward deflection); (2) electrocardiogram; (3) ballistocardiogram and (4) time line: a dotted line with .04 seconds between each small interval and 0.2 seconds between each large interval.

The ballistocardiogram may be described as to the regularity and definitiveness of each beat pattern, the relative amplitude of the component waves, the variations with respiration and the constancy of HK time. (Fig. 1.) Figure 2 shows characteristic normal adult ballistocardiograms. Figure 3 is a drawing of an enlarged single beat pattern, identifying each of the strokes to be discussed.

The regularity of the beat pattern is an important attribute in that the pattern is irregular in serious cardiac pathologic disorder. The normal pattern is unchanging in appearance from beat to beat except for slight variations of amplitude with respiration. (Fig. 2.)

The onset of each normal complete pattern is definite although when the rate is rapid, the H wave may be obscured by oscillations from the previous beat. In any case the normal H-I stroke is always obvious. (Fig. 2.)

Each individual stroke comprising the single beat pattern must be studied in its relation to others. For this purpose a baseline can be used. In general the after-waves of the preceding beat present a useful means of determining where the baseline should be drawn. If the rate is slow, there will be no difficulty since the after-waves will be reduced to a straight line. (Fig. 2A.) In more rapid rates the baseline can be drawn with considerable accuracy by observing the os-

* From the Department of Medicine, University of Rochester School of Medicine and Dentistry, and the Medical Clinic of the Strong Memorial and Rochester Municipal Hospitals, Rochester, N. Y. This work was carried out under a contract between the Office of Naval Research and the University of Rochester School of Medicine and Dentistry.

cillations which follow the preceding N peak and determining where the baseline would have been if there were no succeeding beat. (Fig. 2B.)

H Wave. The variation of the H wave from normal to normal is perhaps greater than any other component of the pattern. It may be low or flat or it may be relatively high. (Fig. 2.) Ordinarily the H peak is approximately one-fourth the size of the J peak and less than the I valley. It has been suggested by Hamilton[10] that this first upward deflection is initiated by the apex thrust which occurs during isometric contraction. Figures 4A and 4B show the simultaneous relations of the onset of the H wave to the apex thrust and first heart sound.

I Wave. In the normals observed thus far the I valley has always been less than the J peak, and usually greater than the H peak. It varies in size with different individuals; generally it is approximately one-half the J peak. (Fig. 2.)

The downward I wave may be caused by the footward component of the cardiac recoil accompanying ventricular ejection.[4,10] It can be seen from Figures 4A and 4B that the H-I stroke occurs at the proper time for

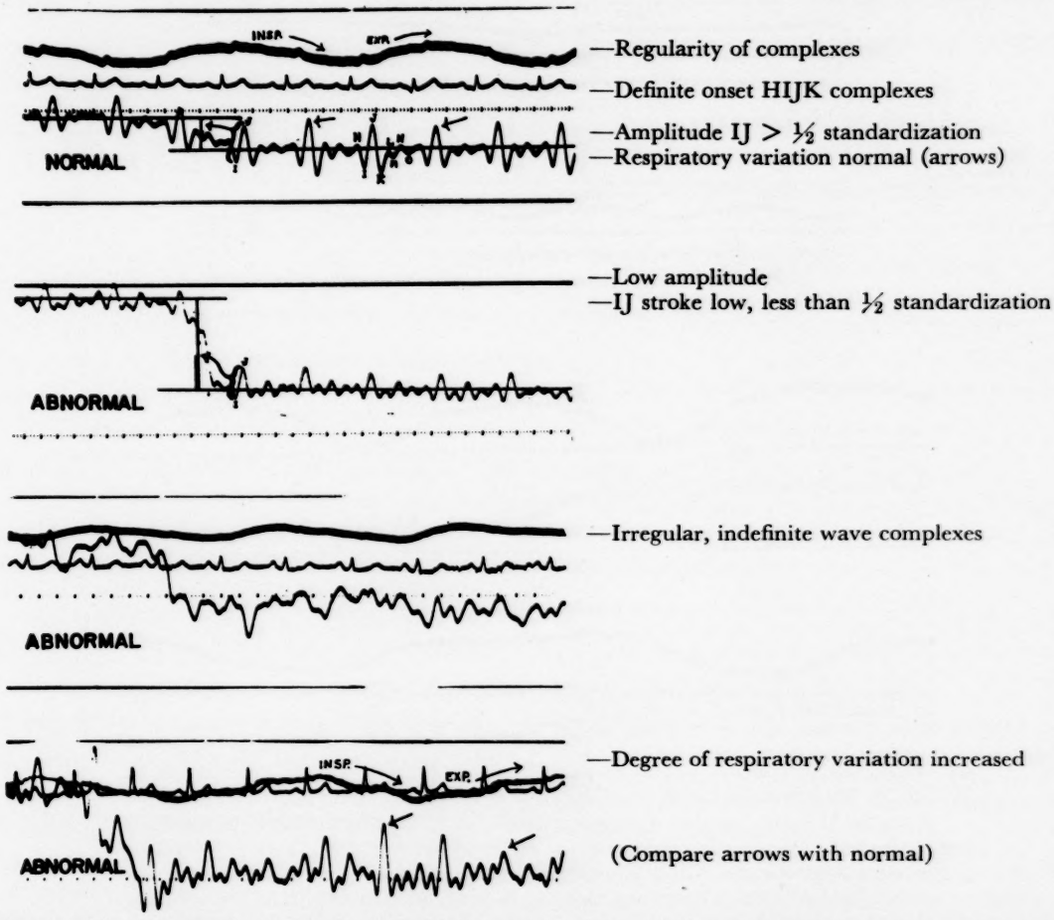

FIG. 1. Empirical criteria in the evaluation of the BCG; a comparison of a normal ballistocardiogram (top record) with three abnormal records. The normal record is characterized by regularity and definitiveness of pattern. Note that the height of the I-J stroke is more than one-half the change in baseline caused by the standardization. There is a respiratory variation of the height of the I-J stroke but it is not marked (arrows). The first abnormal record demonstrates an abnormally low amplitude of the I-J stroke; the height of the I-J stroke is less than half the standardization. This patient has Addison's disease. The second abnormal record demonstrates what is meant by "irregular, indefinite wave patterns." Note that the pattern characteristics change from beat to beat (irregularity), and that the onset of each wave pattern cannot be readily determined (indefinitiveness). The third abnormal record shows a marked respiratory variation of the height of the I-J stroke produced by an abnormal expiratory wave pattern. Compare the expiratory and inspiratory beats with the normal (arrows).

this to be true. Possible further evidence for this premise is offered later under respiratory variation of the ballistocardiogram.

The *J wave* may be due to deceleration of either blood or impulse wave or both by the aortic and pulmonic arches and possibly coincidence if the source of the J wave proves to be deceleration of the impulse wave rather than blood flow. However, the momentum of the impulse wave must in turn be proportional to the actual stroke volume (since the impulse bulge is produced by the blood displaced from the ventricles) so that it is likely that a correlation would exist in any case. Furthermore, the observation that both the total ventricular stroke volume[12,13] and the I-J stroke increase with inspiration lend support to the concept that they are related.

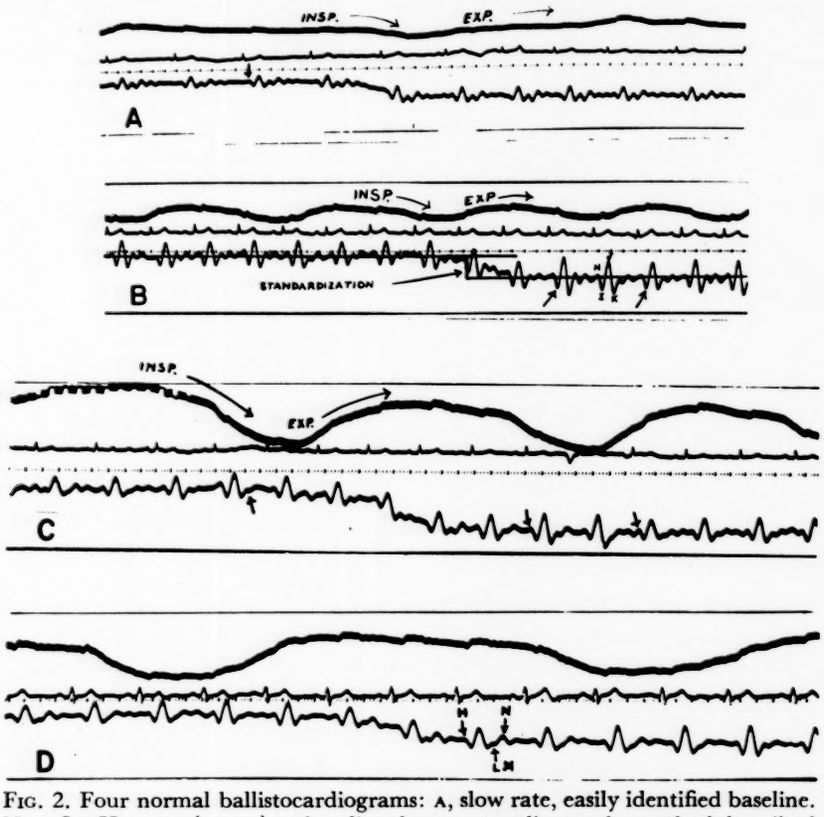

FIG. 2. Four normal ballistocardiograms: A, slow rate, easily identified baseline. Note flat H waves (arrow). B, baseline drawn according to the method described in the text. The standardization is the distance between the two lines. Note the increased amplitude of the I-J stroke with inspiration (arrows). C, first arrow shows flat LM stroke; note the following N peak. Second and third arrows show respiratory variation of the H wave: increase with expiration. D, note flat H peak and flat LM stroke followed by definite N peak (arrows).

the head. It is the highest normal upward deflection and may be regarded as a means of estimating the stroke volume and the forcefulness of cardiac ejection. (Fig. 2.) In normal and abnormal subjects in whom the pattern is regular enough it is possible to arrive at figures for the stroke and minute volumes by Starr's method.[4,5] These are satisfactory for comparative analyses under controlled conditions but are lower than the results obtained with the direct Fick method.[11] The constant ratio of the ballistocardiographic determination of the cardiac output to that obtained by the direct Fick method in normal subjects may be a coin-

However, it is not routinely necessary to compute the cardiac output by such measurements for one can arrive at gross and practical estimates by comparing the I-J stroke with the standardization. The standardization is accomplished by allowing a 280 gm. weight to exert a constant pull upon one end of the table. The resulting shift in

the baseline is then proportional to the sensitivity of the apparatus and useful in computing or estimating the cardiac output. The ratio of the I-J stroke to the standardization is constant for any individual at a given time, regardless of the sensitivity.

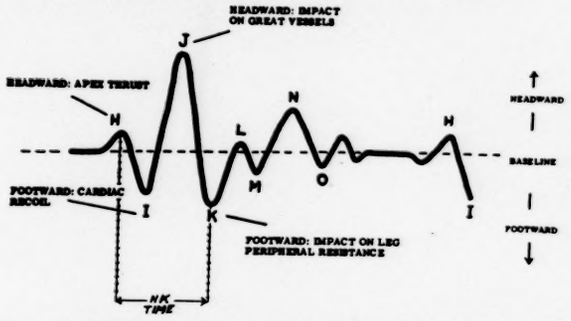

FIG. 3. Drawing of a single ballistocardiogram beat.

In a series of 100 normals, using this method of standardization, we have observed that the ratio of the I-J stroke to the standardization is usually more than 0.5. (Fig. 2.) In large subjects it may be 1.0 or more (Fig. 2B); in small individuals it occasionally is slightly less than 0.5. With this simple method it is possible to approximate cardiac outputs in general terms of low, normal or high. It must be stated, however, that each newly constructed ballistocardiograph will have its own sensitivity characteristics and must be standardized in this respect.

K Wave. The normal K wave is usually as deep as the I wave, with slight variations (Fig. 2); shallowness or marked depth is abnormal. It is possible that the J-K deflection represents the deceleration of the footward traveling impulse wave by the arteriolar peripheral resistance in the legs.[10] Supporting evidence for this will be seen later when it is shown that the K wave is deepened in hypertension and more shallow in hypotension. (Fig. 10.) The K wave increased with inspiration in thirty-two of thirty-nine normals.

The characteristics of the L, M, N, O waves are frequently obscured by rapid heart rates or by phase oscillations. However, it is our opinion that they are probably not all simple oscillations representing a return to the baseline because of the variations observed. (Figs. 2C and 2D.)

HK Time. The HK time is arbitrarily measured from the peak of H to the valley of K (Fig. 3); it can be thought of as proportional to the time interval between the onset of cardiac ejection and the arrival of the impulse wave at the legs. Estimation

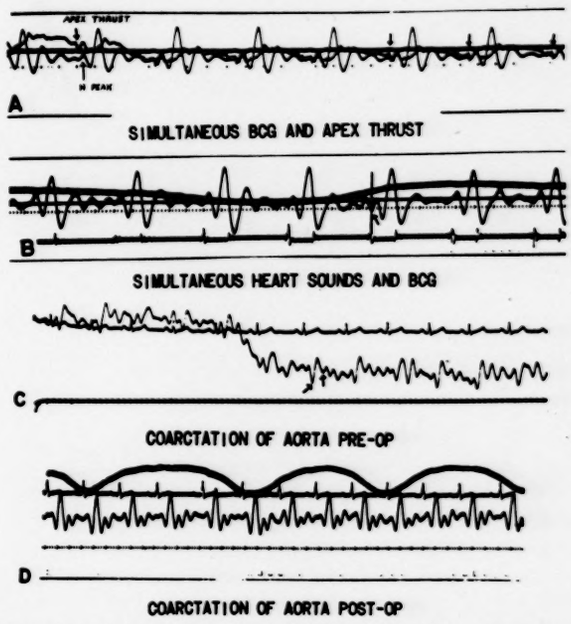

FIG. 4. Records A and B show relationship of apex thrust to H peak. In A the arrows point to the onset of the apex thrust as recorded by a piezo-electric crystal. B, the heart sounds are recorded and the arrow points to a line drawn through the onset of the H peak. Records C and D are taken on a patient before and after operation for coarctation of aorta. In C where the coarctation interferes with transmission of the impulse to the legs the K wave is shallow. In D following surgical repair of the coarctation there is a normal K wave. These records add confirmation to the theory that the K wave is produced by deceleration of the arterial impulse wave by the leg peripheral resistance.

of this time interval is of the same order of magnitude as the actual measurement.

The HK time was measured in forty consecutive normal adults, male and female. It varied from individual to individual but was found to be constant in any one subject to within .01 second. It did not vary with cycle length (Fig. 5A) but showed some relationship to the height of the individual. (Fig. 5B.) This observation is in keeping with the present theory of K wave production.

Respiratory Variation. Respiration affects the ballistocardiogram in at least two ways, namely, it changes the position of the heart with respect to the long axis of the body,

and it produces the changes in blood flow to and from the right and left heart.

If the apex thrust causes the H wave, then the more lateral the heart the more effective the vertical component of the apex thrust will be in producing the H wave. Since the heart becomes more lateral in expiration, one would expect the H wave to increase in expiration. (Fig. 2.) This expiratory increase occurred in 55 per cent of forty adult normals (twenty males, twenty females). However, inspiration increases the total volume of the heart[12] and, therefore, it is likely that the total force of the apex thrust is increased with inspiration. This would tend to counteract the effect of the change in position and may account for the number of subjects in which the H wave showed no change or increased with inspiration.

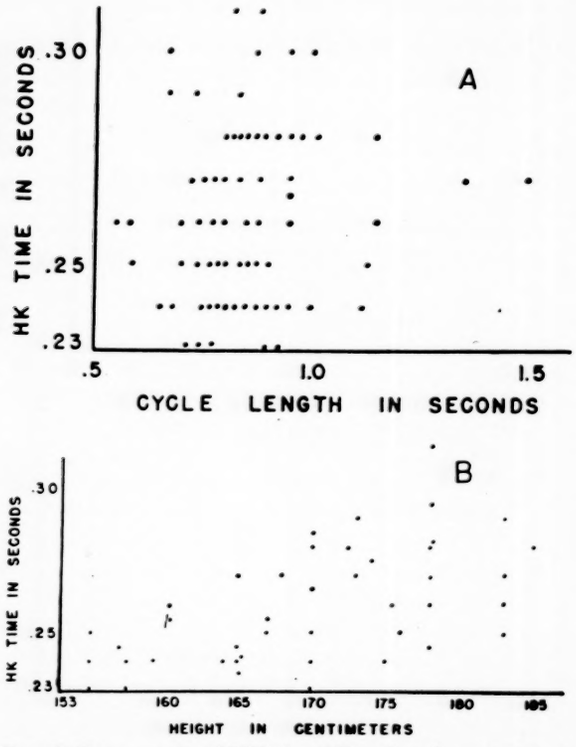

FIG. 5. Two graphs of HK time. The first demonstrates no relationship between HK time and cycle length. The second shows that the HK time tends to increase with height.

If the I wave is produced by cardiac recoil, then one would expect to find normal individuals where the I valley is deeper in inspiration than in expiration since the footward component of the cardiac recoil is more pronounced when the heart is more vertical, i.e., in inspiration. Figure 2c shows examples of this inspiratory increase of the I wave which occurred in 85 per cent of forty adults. Another cause for the increased H-I stroke in inspiration might be deduced from the experiments reported by Boyd and Patras[12] which show that the combined diastolic filling and combined stroke volumes of left and right heart are greater in inspiration. Therefore, one would expect that the effect of heart recoil would be greater in inspiration.

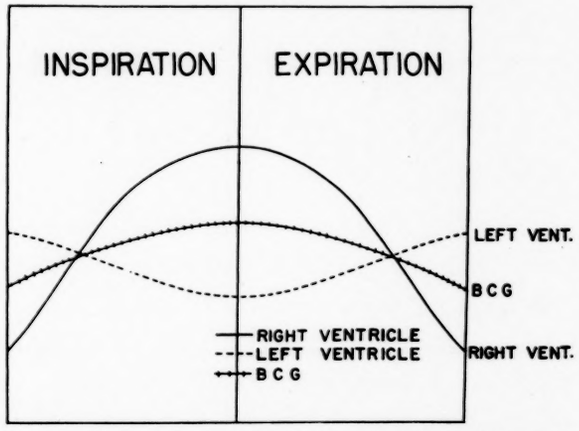

FIG. 6. Schematic drawing comparing the respiratory variation of the ventricular stroke volumes (after Shuler et al.[13]) with the ballistocardiogram stroke volume variation. Note that the right heart variation is greater than the left; the variation of the total stroke volume will therefore increase with inspiration, thus paralleling the ballistocardiogram respiratory changes.

Inspection of forty normal ballistocardiograms revealed that in thirty-nine of forty cases the J peak was greater in inspiration than in expiration. (Fig. 2.) The increased I-J stroke in inspiration is probably related to the changes in cardiac output with respiration and may be explained in the following manner: In 1942 Shuler and coworkers confirmed the findings of Boyd and Patras and further showed that although the total ventricular volume increased with inspiration, the left ventricular stroke volume decreased.[13] They also showed that the right heart stroke volume variations were greater than those of the left heart. Thus the variation of the right heart overshadows that of the left and the total stroke volume variation parallels that of the right heart.

(Fig. 6.) This was further illustrated by Starr[14] who reversed the I-J stroke respiratory variation when he reversed the right heart respiratory variation by forcing inspiration with intermittent positive pressure breathing.

the right heart stroke volume to decrease simultaneously with a left heart increase (during expiration). A more detailed discussion of normal and abnormal respiratory variation of the I-J stroke has been given.[17]

The total relative cardiac output meas-

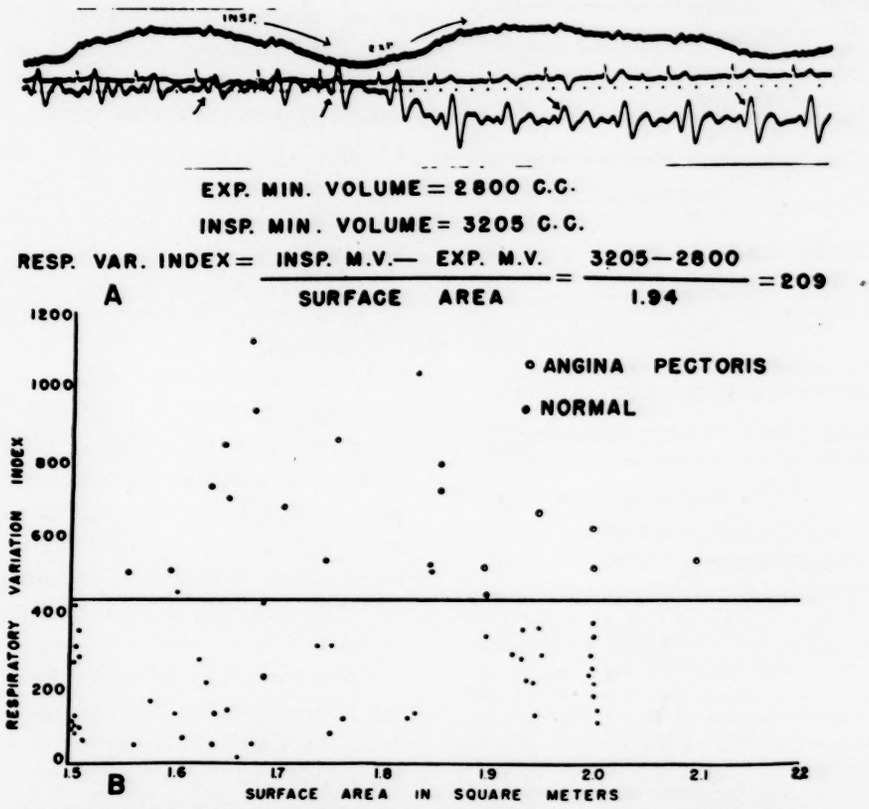

FIG. 7. Using the inspiratory and expiratory beats pointed out by arrows on the top pattern, the minute volume for each phase of respiration can be calculated. From these figures the respiratory variation index is computed by subtracting the expiratory minute volume from the inspiratory minute volume. This figure is then divided by the surface area in square meters to allow comparison of large and small individuals. The graph demonstrates the increased respiratory variation to be found in angina pectoris.

The fact that the left heart stroke volume increases in expiration while the right heart output decreases may be understood and deduced when one considers the effect of expiration upon the venous return to left and right auricles. Expiration increases the intrapleural (intrathoracic) pressure. The increased intrapleural pressure impedes the return of systemic venous blood to the right auricle while it increases the return of pulmonary blood to the left auricle. The ventricles can only eject as much blood as they get, and one would therefore expect

urements of both stroke and minute volume can be made in inspiration and in expiration by applying Starr's formula to the proper beats.[4] It is apparent from the latter discussion that the inspiratory total minute volume figures will be higher than the expiratory figures. This variation may be termed the ballistocardiogram respiratory variation. One of us (V. D.) has devised a method for arriving at what may be called the "ballistocardiogram respiratory variation index," which falls into certain limiting figures for the normal adult.

The ballistocardiogram respiratory variation index is determined in the following manner: In several consecutive normal respirations, the average of the largest inspiratory beats is used to compute the inspiratory minute volume, and similarly

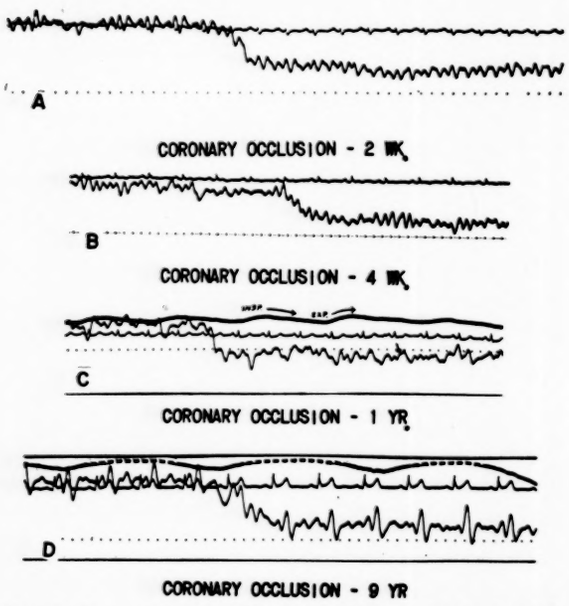

FIG. 8. Four patterns taken on different patients with coronary occlusion. A was taken two weeks after the occlusion. B was taken four weeks after an occlusion. C was taken 1 year after an occlusion. Note the abnormal patterns of low amplitude. D was taken nine years after an occlusion. Note the regularity and definitiveness of pattern, with fairly good amplitude. C and D demonstrate the usefulness of the ballistocardiogram in evaluating the post-occlusion status.

the average of the smallest expiratory beats is used to compute the expiratory minute volume. The difference between these two figures is divided by the surface area of the individual and the result is expressed in terms of cubic centimeters per square meter body surface area per minute. Figure 7 shows an example of the computation. The respiratory variation index of fifty normal adults between the ages of twenty to seventy has been measured. The results are shown. (Fig. 7.) Note that although the index tends to increase with surface area, with one exception, all normals are below 450 and all but three fall below 400. It must be stated that the bulk of the series of patients were between the ages of twenty-five and thirty-five. However, normals within the older age groups are included and thus far all those measured are within the limits described before.

CLINICAL VALUE OF THE BALLISTOCARDIOGRAM

It is the purpose of this section to show in what ways abnormal ballistocardiograms may differ from normal records and to demonstrate how these differences may be used in the diagnosis and evaluation of various clinical states. The descriptions obtained in the normal can be applied to the abnormal. (Fig. 1.) Each tracing can be studied from the point of view of amplitude, regularity, definitiveness, variations of H, I, J, K waves, the respiratory variation and HK waves.

Low amplitude of pattern may occur in any situation in which the output is low and/or the ventricular muscle is weak. (Figs. 8, 9 and 10.) In general, irregularity and indefinitiveness of pattern indicates serious impairment of ventricular function, such as might occur with infarction (Fig. 8), failure (Fig. 9), pericarditis or myocarditis. (Fig. 9.)

Abnormalities of individual strokes occur in more specific situations such as hypotension (Fig. 10), hypertension (Figs. 9D and 10B), angina pectoris (Fig. 11C), coarctation of the aorta (Fig. 10C) and hypertensive heart disease. (Fig. 9D.)

Abnormal (i.e., increased) respiratory variation occurs particularly with the syndrome of angina pectoris but also may be seen with other conditions such as hypertension (Fig. 11), sympathectomy (Fig. 12), pulmonary emphysema (Fig. 11) and in normal subjects with resistance breathing. (Fig. 11.) The respiratory variation index has been measured in cases of clinically appraised coronary insufficiency with normal blood pressure and without an occlusion. It was found that the index was higher than 450 in all cases and higher than 500 in all but one. (Fig. 7.) It has been reported that this finding offers another aid in the evaluation of the patient with the angina pectoris syndrome.[15] Convenient

empirical classification has also been described[15] allowing for gross grading of degrees of abnormality, namely, Grades I, II, III and IV.

Variation of the HK time usually is present in those instances in which the pattern is irregular and indefinite, i.e., infarction, failure or myocarditis.

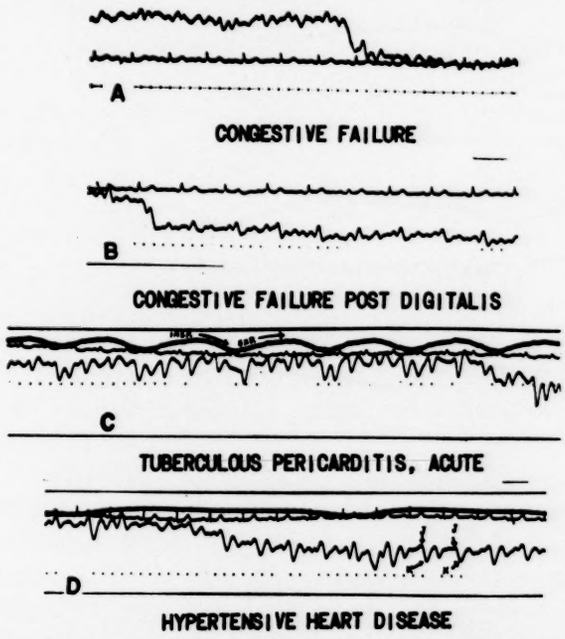

FIG. 9. A and B are serial tracings on a sixty-two year old woman who had congestive failure. Tracing A shows the typical irregular, indefinite pattern of low amplitude. B was taken after digitalization. Note the improved amplitude and the return of definitiveness and regularity. Tracing C is a record of a forty-seven year old woman who presented a diagnostic problem. She had fever, leukocytosis, acute right upper quadrant pain, with tenderness and tachycardia. The very abnormal ballistocardiogram assisted in making the final diagnosis of tuberculous pericarditis. Note the irregular, indefinite pattern of low amplitude. Tracing D represents typical findings in severe hypertensive cardiovascular disease. Note the very low amplitude in expiration with shallow I-J, deep K waves (arrows).

Examples of these abnormalities in cases in which the ballistocardiogram was found to be of value, either in making the diagnosis or in evaluating the condition of the patient after the diagnosis was made, are presented as follows:

Mrs. P. was a sixty-three year old neurotic woman who complained of dyspnea on exertion. Neither the electrocardiogram nor physical findings were in themselves diagnostic. The ballistocardiogram revealed an abnormal pattern of low amplitude, with indications of irregularity suggesting impairment of mechanical heart action. (Fig. 9A.) She was digitalized and improved. Figure 9B was taken after digitaliza-

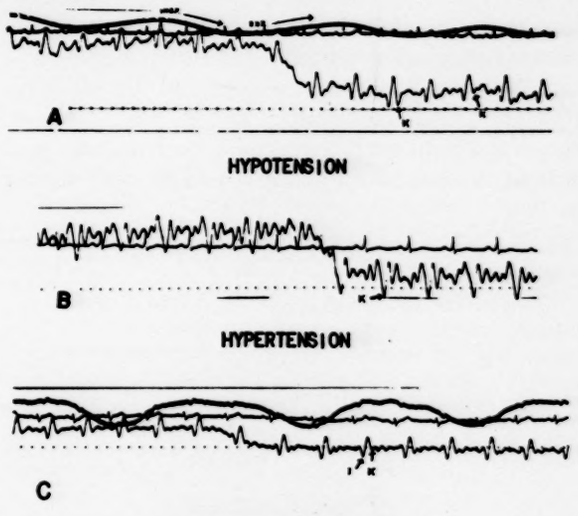

FIG. 10. Tracing A shows the shallow K wave that is seen in cases of hypotension (arrows). B demonstrates the deep K wave that occurs with hypertension. C is the pattern of a twenty-two year old male with coarctation of the aorta. Note the shallow K and deep I wave (arrows).

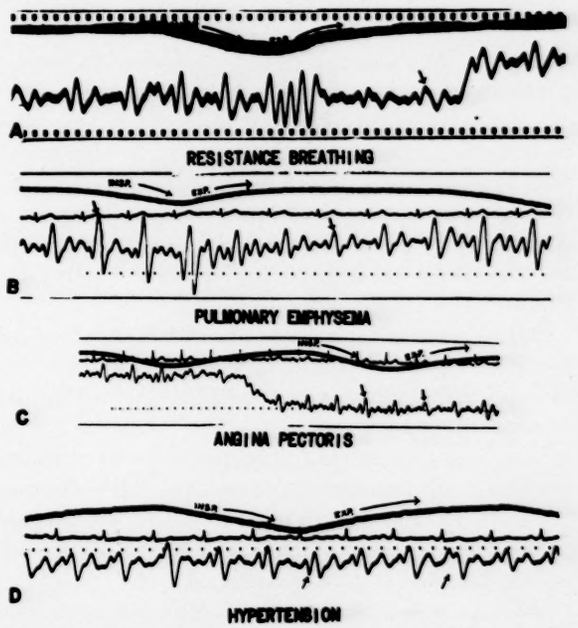

FIG. 11. Four examples of patterns with increased respiratory variation. Tracing A was taken on a normal subject during resistance breathing. Note the abnormally low patterns in expiration. B is on a patient with emphysema. C is the pattern of a man with angina pectoris. D represents the increased variation that can be seen in hypertension.

tion and showed an improved output and a more normal-appearing pattern.

I. T. was a forty-seven year old female who had fever, leukocytosis, acute right upper quadrant pain with tenderness, tachycardia and transient auricular fibrillation. The differential diagnosis lay between acute cholecystitis, myocardial infarction or severe myocarditis. The electrocardiogram was not diagnostic. A ballistocardiogram revealed a markedly abnormal pattern which was irregular and indefinite, indicating poor mechanical heart action. (Fig. 9C.) This finding aided in the decision to postpone surgery long enough to arrive at the ultimate diagnosis of tuberculous pericarditis.

Mr. Y. was a forty-five year old man who had fever, purpura, malaise and tachycardia. The electrocardiograms were within normal limits except for increased rate. The ballistocardiogram was abnormal, interpreted as showing evidence of myocardial damage. This finding assisted in the diagnosis of acute rheumatic myocarditis. The ballistocardiogram improved as the clinical state improved.

Mr. E. was a twenty-eight year old man who had beriberi, with both clinical and x-ray evidence of cardiac enlargement. Serial ballistocardiograms taken before, during and after treatment with vitamin B proved to be a simple method of following the cardiac status and improvement with therapy. Electrocardiograms taken at the same time showed no significant changes other than a slowing of the rate.

The ballistocardiogram is useful in evaluating the status of the heart muscle after an infarction. Figure 8 shows records taken in four patients who had a coronary occlusion.

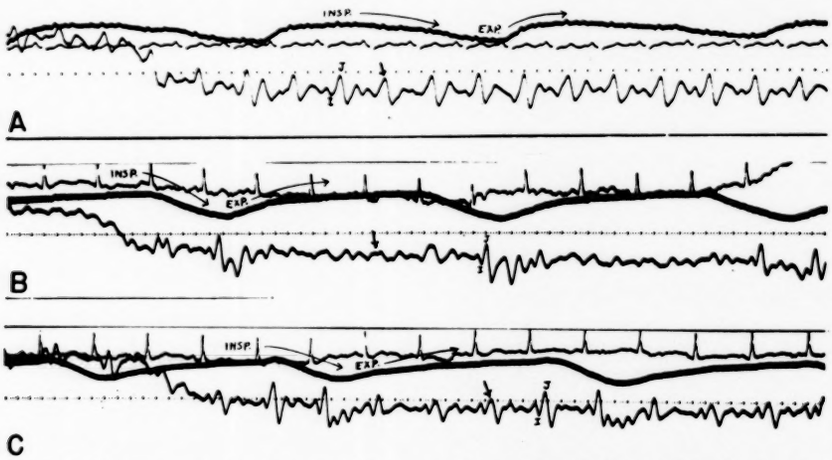

FIG. 12. Three records taken on a hypertensive patient before (A) and after (B and C) dorsal sympathectomy. Tracing B was taken without abdominal binders or elastic stockings. Note the marked decrease of amplitude of the expiratory patterns (arrow) as compared with (A), and the consequent increase of respiratory variation. Tracing (C) was taken immediately after tracing (B) but with tight abdominal support and elastic stockings applied. Note the increase in the amplitude of the expiratory beats (arrow) as compared with (B). The sensitivity of the ballistocardiograph amplifier was kept constant for tracings B and C.

Mr. O. was a fifty-one year old man who had undergone severe mental and emotional strain at a time when he was working long hours. Precordial pain developed. Electrocardiograms and physical findings were not helpful. A ballistocardiogram revealed an abnormal tracing with an increased respiratory variation index of 655 cc. square meter body surface area per minute which was evidence for angina pectoris.

Mr. M. was a forty-four year old man who had hypertension for a period of several years. Because of an increase in symptoms he was being evaluated for bilateral sympathectomy. The electrocardiogram primarily showed left axis deviation; the ballistocardiogram showed low amplitude, with shallow I, high I-J take-off and deep K waves particularly in expiration. (Fig. 9D.) Contrast this record with that of Figure 12A in which the patient was a thirty-three year old female with a two-year history of hypertension.

Mr. G. was a twenty-two year old male who had x-ray signs suggestive of coarctation of the aorta. Blood pressure in the upper extremities was 160/90. The blood pressure in the legs was

not obtained by usual technics. The electrocardiogram was within normal limits. A ballistocardiogram revealed a pattern characteristic of coarctation of the aorta (Fig. 10c), e.g., deep I and shallow, almost flat plateau K waves.

SUMMARY

A discussion of the ballistocardiogram with analysis of individual wave forms and their variation in normal and abnormal subjects is presented. Most of the tracings include simultaneously recorded events of the respiratory cycle, the electrocardiogram and the ballistocardiogram.

Evidence is presented that analysis of the ballistocardiogram wave complexes from cycle to cycle, and as influenced by respiration, assists in the establishment of various diagnoses and in following the course of certain disease processes.

Examples of the empirical usefulness of this instrument in assaying myocardial function, angina pectoris syndrome, congenital cardiovascular abnormalities and degenerative cardiovascular disease are given.

It is acknowledged that further study is necessary to determine more specifically the causes of each of the wave complexes.

Acknowledgment: Appreciation is expressed to Dr. William S. McCann for his advice and counsel in the planning and conducting of experiments and also for his critical review of manuscript. The technical assistance of Miss Elaine E. MacDowell is gratefully acknowledged.

Addendum: Since compilation of this paper fifty patients with coronary insufficiency and six patients with coarctation of the aorta have been studied with respect to the ballistocardiogram (and the respiratory variation index in the case of coronary insufficiency). These have been reported in separate articles.[15,16]

REFERENCES

1. Gordon, J. W. On certain molar movements of the human body produced by the circulation of the blood. *J. Anat. & Physiol.*, 11: 553, 1877.
2. Henderson, Y. The mass movements of the circulation as shown by a recoil curve. *Am. J. Physiol.*, 14: 287, 1905.
3. Heald, and Tucker. The recoil curves as shown by the hot wire microphone. *Proc. Roy. Soc., London*, 93: 281, 298, 1922.
4. Starr, I., Rawson, A. and Schroeder, H., Joseph, N. Studies on estimation of cardiac output in man and of abnormalities in cardiac function, from heart's recoil and blood impacts. *Am. J. Physiol.*, 127. 1, 1939.
5. Starr, I. and Schroeder, H. Ballistocardiogram—normal standards, abnormalities commonly found in disease of heart and circulation, and their significance. *J. Clin. Investigation*, 19: 437, 1940.
6. Starr, I. Clinical studies with ballistocardiograph; in congestive failure, on digitalis action, on changes in ballistic form and in certain acute experiments. *Am. J. M. Sc.*, 202: 469, 1941.
7. Starr, I. Studies with ballistocardiograph in acute cardiac infarction and chronic angina pectoris. *Am. Heart J.*, 25: 81, 1943.
8. Starr, I. On the later development of heart disease in apparently healthy persons with abnormal ballistocardiograms. Eight to ten years after histories of ninety persons over forty years of age. *Am. J. M. Sc.*, 214: 233, 1947.
9. Brown, H. Jr. and Pearson, R. A new electronic method for simultaneous recording of the ballistocardiograph and electrocardiograph. *Am. Heart J.*, 35: 756, 1948.
10. Hamilton, W. F., Remington, J. W. and Dow, P. Relationship between cardiac ejection curve and ballistocardiographic forces. *Am. J. Physiol.*, 144: 557, 1945.
11. Cournand, A. Measurements of cardiac output in man using right heart catheterization, description of technique, discussion of validity and of place in study in circulation. *Federation Proc.*, 4: 207, 1945.
12. Boyd, T. E. and Patras, M. Variations in filling and output of ventricles with phases of respiration. *Am. J. Physiol.*, 134: 74, 1941.
13. Shuler, R., Ensor, C., Gunning, R., Moss, W. and Johnson, V. Differential effects of respiration on left and right ventricles. *Am. J. Physiol.*, 137: 602, 1942.
14. Starr, I. and Friedland, C. On cause of respiratory variation of ballistocardiogram with note on sinus arrhythmia. *J. Clin. Investigation*, 25: 53, 1946.
15. Brown, H. R., Jr., Hoffman, M. J. and de Lalla, V., Jr. Ballistocardiographic findings in patients with symptoms of angina pectoris. *Circulation*, 1: 132, 1950.
16. Brown, H. R., Jr., Hoffman, M. J. and de Lalla, V., Jr. Ballistocardiograms in coarctation of the aorta. *New England J. Med.*, 240: 715, 1949.
17. de Lalla, V., Jr. and Brown, H. R., Jr. The respiratory variation of the ballistocardiogram. *Am. J. Med.*, 10: 728, 1951.

Respiratory Variation of the Ballistocardiogram*

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THE empirical observation of the respiratory variation of the ballistocardiogram has been reported in normal and abnormal subjects.[1–3] When simultaneous respiration and ballistocardiogram tracings are recorded in a normal subject, it is found that the height of the IJ stroke will increase with inspiration and decrease with expiration. (Fig. 1.) The normal range of this variation has been reported in terms of the ballistocardiogram respiratory variation index by Brown and de Lalla.[2]

This paper will present a discussion of the normal variation and certain evidence to show that an abnormal (increased) variation may be associated with a diminution of the pulmonary blood pool.

It is pertinent at this point to discuss briefly the pulmonary blood pool. It has been shown by several observers that a pulmonary pool exists and that it is of considerable magnitude.[4–6] This large pool of intravascular blood probably acts as a cushion between the right and left ventricles and prevents the relatively drastic changes of the right heart output that occur with changes in intrapleural pressure from being transmitted to the systemic circulation via the left ventricle. This mechanism is augmented by the same intrathoracic respiratory pressure changes that cause the right heart variation. When the intrathoracic (intrapleural) pressure is increased by expiration, the venous return to the right heart is diminished, thereby decreasing the output; but the venous return to the left heart is enhanced, thereby increasing the left heart output at a time when the output of the right heart is diminished. The reverse occurs with inspiration.[7–8]

The importance of these effects can be seen when one considers that the right heart output may frequently drop to critical levels during forced expirations, a bout of coughing and prolonged sighing. If the cushioning effect of the pulmonary pool were not present, it is likely that syncope due to cerebral anoxia would supervene since the left ventricular output would also be seriously diminished. (It is possible that this is the sequence of events that occurs in patients with tussive syncope when bouts of coughing may be of such a nature as to exhaust the pulmonary pool when the pulmonary pool is already critically low due to other causes.)

Shuler et al. have demonstrated that the total ventricular output increases with inspiration and decreases with expiration; this is to be expected since the variation of the right heart is greater than that of the left; thus the total variation will parallel that of the right heart, i.e., diminish with expiration, increase with inspiration.[8] It is reasonable to assume that one of the factors responsible for the magnitude of the IJ stroke is the total stroke volume.[1–3,9,10] The observation that the respiratory variation of the IJ stroke is in the same direction as the variation of the total ventricular stroke volume is in keeping with this concept.

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Although our interest was stimulated by the ballistocardiogram finding of increased respiratory variation in patients with angina pectoris,[2,3] it was the observation that a marked increase in the ballistocardiogram respiratory variation was produced in hypertensive patients subsequent to a bilateral dorsal sympathectomy that led to the following experimental work:

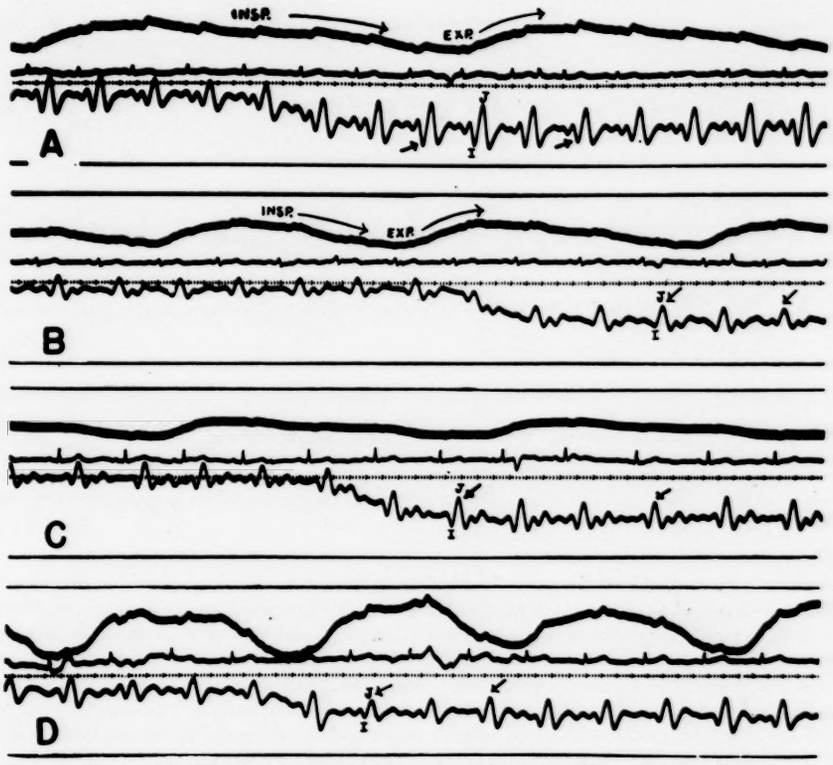

FIG. 1. Normal ballistocardiogram; four normal adults. Note the regularity and definity of pattern, and the respiratory variation of the IJ stroke (increase in inspiration).

Destruction of the dorsal sympathetic chains results in pooling of large amounts of blood in the affected areas (splanchnic and legs). This pooling diminishes the venous return to the right heart so that in many patients postural (standing) hypotension and syncope develop. These individuals also show an increase in the ballistocardiogram respiratory variation postsympathectomy, together with a very low expiratory amplitude of the IJ stroke. (Fig. 2.) It is possible that the increased pooling in the splanchnic and leg areas decreased the pulmonary pool to such an extent that it no longer effectively cushioned the respiratory changes of the right heart output and, therefore, the output of the left heart more nearly paralleled that of the right. This would account for the observation that it is the expiratory beats which are abnormally low since the right heart output diminishes with expiration. (Fig. 2B.) Under these circumstances the respiratory variation of the total output would more closely reflect the right heart respiratory variation, producing the changes observed in the ballistocardiogram.

Evidence for this was derived by taking ballistocardiograms on sympathectomized patients with and without supportive abdominal belt and stockings. Presumably these binders prevent leg and splanchnic blood pooling to a large extent and maintain the blood pressure above syncope levels. This effect is illustrated by blood pressure records taken on a patient, Mr. R., who experienced standing hypotension and syncope following a bilateral sympathectomy. His blood pressure was 200/110 lying down but dropped to 80/65 within four minutes

of passive standing. When he was placed in a rubber boot filled with water up to the iliac crests, he was able to stand passively for fifteen minutes and his blood pressure never fell below 120/80.

Figure 2 shows how the respiratory variation increased in a patient following bilateral dorsal sympathectomy. (Compare Fig. 2A with 2B.) Hypotension and syncope developed when the patient was standing. When a tight abdominal binder and elastic stockings were applied, she was more comfortable and was able to stand for longer periods of time without syncope. A ballistocardiogram taken with these supports on showed that the respiratory variation promptly decreased (approached normal). (Compare Fig. 2B with 2C.) Thus the respiratory variation increased when the pulmonary pool diminished (following bilateral sympathectomy and the subsequent splanchnic and leg pooling), and decreased when the pulmonary pool was increased (following application of binders).

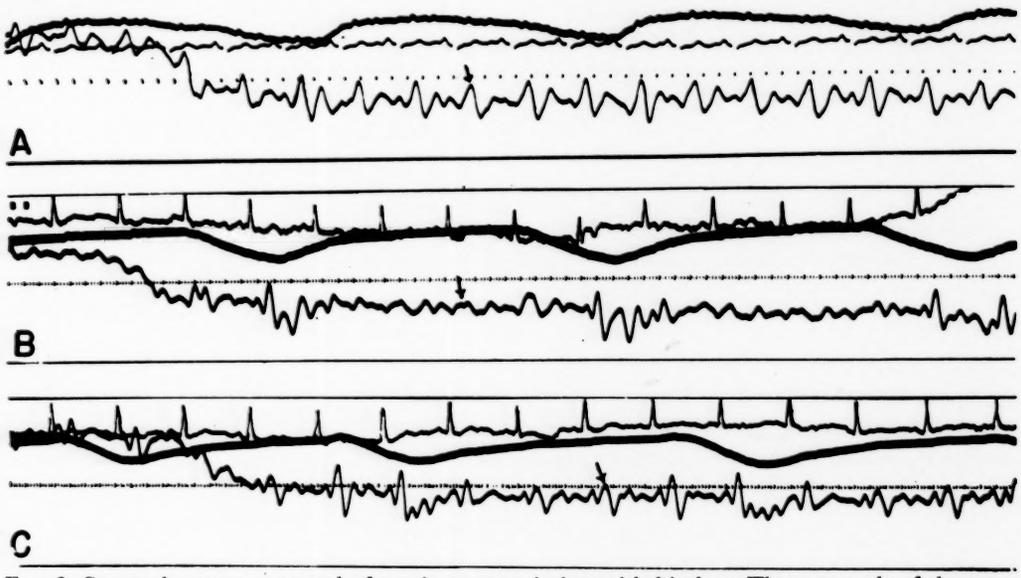

FIG. 2. Sympathectomy, reversal of respiratory variation with binders. Three records of the same patient taken before (A) and after sympathectomy (B and C). A, ballistocardiogram of a hypertensive patient before dorsal sympathectomy. B, tracing of same patient as in A taken soon after a bilateral dorsal sympathectomy. Note the marked diminution in amplitude of the IJ stroke in expiration causing an increased (abnormal) respiratory variation. Compare expiratory beats in A with B (arrows). C, ballistocardiogram of same patient taken same day as in B, but after the application of abdominal and leg binders. Note the increased amplitude of the expiratory complexes (compare B with C arrows) and the more normal (decreased) respiratory variation.

Interestingly enough, in an occasional patient postsympathectomy precordial chest pain develops on standing which is relieved by slight exertion but is especially relieved by lying down with the legs elevated. Presumably, the pain derives from insufficient coronary blood flow due to a very low left ventricular output. One such case was studied by us; her ballistocardiogram showed an abnormal pattern of very low amplitude. When an abdominal binder was applied, she felt more comfortable and the ballistocardiogram amplitude increased. This observation led to a study of the effects of an abdominal binder in patients with angina pectoris.[3]

The possible causative relationship between a diminished pulmonary pool and coronary insufficiency is intriguing. It has been construed by us that the pulmonary pool is diminished in those individuals who have coronary insufficiency with an increased ballistocardiogram respiratory variation. It is accordingly conceivable that in certain cases the primary cause of insufficient coronary blood flow is the diminished pulmonary blood pool which produces a critical diminution of the left ventricular

output in expiration. Under these circumstances the coronary spasm that might be obtained would be a compensatory effort to maintain coronary artery blood pressure. During this period the disease process might be reversible. However, later it might be expected that sclerosis would develop, producing an irreversible state.

Since so many patients with coronary insufficiency complain of discomfort and pain in cold weather, it was considered of interest to determine the effect upon the ballistocardiogram of sudden exposure of the body to a cold environment. Accordingly, five normal male adults were rested upon the ballistocardiogram table; and after control tracings had been taken, they were exposed to a room temperature of 60°F. by quickly removing the blankets which had been covering them. Serial ballistocardiographic records were taken, together with blood pressures, up to the point of shivering. In all cases the ballistocardiogram changed in a manner that increased the respiratory variation, producing a pattern much like that seen in coronary insufficiency and in resistance breathing. (Fig. 3.) The increased respiratory variation noted might be due to a reflex producing either peripheral pooling of blood, increased pulmonary resistance to breathing or both.

A fifty-one year old male, who had been experiencing precordial pain for eighteen months and who complained of pain in the cold, was similarly exposed to a room temperature of 60°F. His control tracings showed a low output with an abnormal pattern and an increased respiratory variation. Within thirty seconds of exposure to the cold his pattern had decreased in amplitude, indicating a still lower cardiac output, and his respiratory variation had increased. Within one minute he began to experience precordial pain and the experiment was discontinued. Upon warming, his pain diminished, then disappeared and his tracing improved. Anxiety may have played a role in the production of pain. However, whatever the cause, there was an associated decrease in amplitude and increase in the respiratory variation of the ballistocardiogram.

An increased respiratory variation was

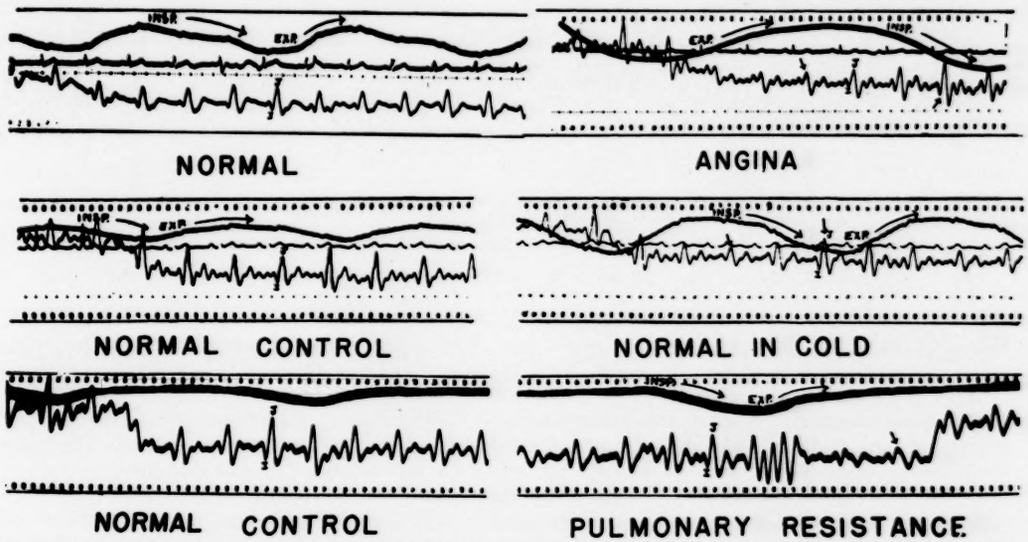

FIG. 3. Six tracings comparing normals (left hand records) with coronary insufficiency (upper right record), normal suddenly exposed to cold of 60°F. (middle right record), and normal breathing through a resistance (lowest right record). The middle records are on the same normal male adult, before exposure to cold (left hand record) and after one minute of exposure to cold (right hand record). The two lowest records are similarly on the same normal male adult before (right hand record) and thirty seconds after resistance breathing was started (left hand record). Note the similarity of pattern in each of the right hand records: increased respiratory variation, with shallow I, deep K waves appearing in expiration (arrows).

also observed in patients with emphysema. This was interpreted as simply an exaggeration of the normal events produced by the increased respiratory intrapleural pressure variations that were present in these patients, i.e., increased negative pressures on inspiration and increased positive pressure on expiration.[11,12] Thus the effects of respiration on the venous return to both right and left heart would be exaggerated and, therefore, the output variation would be greater. Also, since expiration (in time) usually occupies 60 to 70 per cent of the respiratory cycle in these patients, it might be deduced that the increased intrapulmonary positive pressure that is obtained in expiration would diminish the pulmonary pool much as positive pressure breathing does.[5]

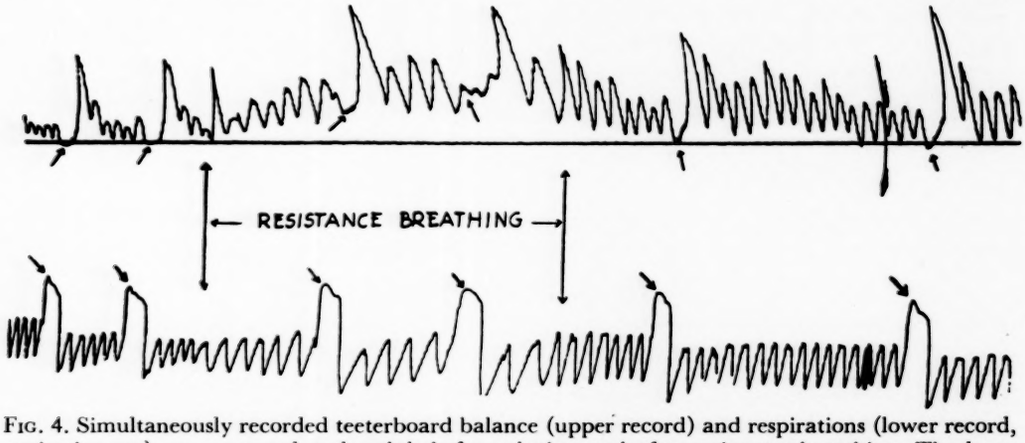

FIG. 4. Simultaneously recorded teeterboard balance (upper record) and respirations (lower record, expiration up) on a normal male adult before, during and after resistance breathing. The large undulations of the teeterboard balance are caused by the movement of the diaphragm with respiration; the footward inspiratory movement of the diaphragm causes a footward shift of weight of the teeterboard (upward deflection). The arrows point to held forced expirations; note that the teeterboard undulations stop and the pointer writes a relatively straight line. This short baseline reflects the distribution of blood. Note that during resistance breathing the teeterboard becomes foot heavy (upward deflection), and that the expiratory baselines (arrows) remain higher than either the control or recovery periods even though the diaphragm presumably occupied the same position in all cases. This is taken to mean that resistance breathing caused a shift of blood in a footward direction.

This theory was partially confirmed by the work of Cain[13] who had five normal subjects breathe through a resistance. He reported that the ballistocardiogram respiratory variation was increased immediately upon the start of resistance breathing which increased the alveolar pressure in expiration and decreased it in inspiration. (Fig. 3.)

A further attempt was made to determine whether any shift in pulmonary blood pool also occurred when breathing through a resistance. Accordingly, the same five subjects who showed an increased respiratory variation with resistance breathing were balanced on a teeterboard using the method described by Fenn and co-workers.[5] After a suitable baseline had been obtained, the resistance was turned on. An immediate footward shift of weight occurred in each case. However, it is possible that the diaphragm shifts downward during resistance breathing and in doing so might have caused all of the footward shift observed. Therefore, one of the subjects who was particularly trained and adept at controlling diaphragm movements was allowed to hold a complete forced expiration several times during the control period, resistance breathing period and recovery period. By this means it was thought that the diaphragm would be fixed in a constant position and its effect on the teeterboard eliminated during those brief periods of complete expiration. Comparison of the teeterboard levels during held expiration showed that a footward shift of weight had occurred with resistance breathing which presumably was independent of the position

of the diaphragm. (Fig. 4.) This footward shift may be interpreted to mean that during resistance breathing blood is driven out of the pulmonary pool and that most of it is taken up by the splanchnic and leg pools. Therefore, it seems reasonable to assume that during resistance breathing a diminution of the pulmonary blood pool occurred at the same time that the ballistocardiogram respiratory variation increased.

SUMMARY

Upon the basis of the aforementioned series of experiments it might be deduced that an increased respiratory variation may very likely be associated with a diminution in the pulmonary blood pool and from the evidence at hand seems to be caused by this diminution. The decrease in the pulmonary pool could be caused either by increased intrapulmonary pressure on expiration, such as occurs during resistance breathing, or by an increase in the peripheral and splanchnic blood pools, such as occurs following a bilateral dorsal sympathectomy. It is also possible that, in certain cases at least, coronary insufficiency might be secondary to a critically low left ventricular output caused by increased peripheral pooling and a consequent decreased pulmonary pool.

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REFERENCES

1. Starr, I. and Friedlan, C. On cause of respiratory variation of ballistocardiogram with note on sinus arrhythmia. *J. Clin. Investigation*, 25: 53, 1946.
2. Brown, H. R., Jr. and de Lalla, V., Jr. The ballistocardiogram description and clinical use. *Am. J. Med.*, 9: 718, 1950.
3. Brown, H. R., Jr., Hoffman, M. J. and de Lalla V., Jr. Ballistocardiographic findings in patients with symptoms of angina pectoris. *Circulation*, 1: 132, 1950.
4. Best, C. H. and Taylor, N. B. The physiological basis of medical practice. 4: 283, 1945.
5. Fenn, W., Otis, A., Rahn, H., Chadwick, L. and Hegnauer, A. Displacement of blood from lungs by pressure breathing. *Am. J. Physiol.*, 151: 258, 1947.
6. Visscher, M. B. Capacity changes in pulmonary vascular bed with respiratory cycle. *Federation Proc.*, 7: 128, 1948.
7. Boyd, T. C. and Patras, M. Variations in filling and output of ventricles with phases of respiration. *Am. J. Physiol.*, 134: 74, 1941.
8. Shuler, R., Ensor, C., Gunning, R., Moss, W. and Johnson, V. Differential effects of respiration on left and right ventricles. *Am. J. Physiol.*, 137: 602, 1942.
9. Starr, I., Rawson, A., Schroeder, H. and Joseph, N. Studies on estimation of cardiac output in man and abnormalities of cardiac function, from heart's recoil and blood impacts. *Am. J. Physiol.*, 127: 1, 1939.
10. Hamilton, W. F., Remington, J. W. and Dow, P. Relationship between cardiac ejection curve and ballistocardiographic forces. *Am. J. Physiol.*, 144: 557, 1945.
11. Paine, J. R. Clinical measurement of pulmonary elasticity. *J. Thoracic Surg.*, 9: 550, 1940.
12. Dean, R. B. and Visscher, M. B. The kinetics of lung ventilation. *Am. J. Physiol.*, 134: 450, 1941.
13. Cain, C. C. and Otis, A. B. Some physiologic effects resulting from added resistance to respiration. *J. Aviation Med.*, 20: 149, 1949.

Hypertension and Renal Dynamics in Aortic Coarctation*

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THERE is considerable disagreement as to whether the changes in blood pressure observed in coarctation of the aorta can be explained solely by the mechanical effects of the lesion. The purpose of this paper is to review critically the controversial literature concerning the genesis of these changes in blood pressure and to determine the role of the kidney by comparison of the renal dynamics before and after operative correction of the obstruction.

Discussion of the blood pressure in coarctation may, for convenience, be divided into two sections, namely, the alterations in the area above the constriction and those below. In the upper extremities hypertension is the rule. Practically all of the 217 cases reviewed by Steele[1] in 1941 showed systolic hypertension and nearly one-half had diastolic pressure over 100. The mean pressure in the brachial arteries is therefore almost always elevated. This hypertension would appear to be caused by the increased resistance to blood flow offered by the constricted area and the collaterals. Experimentally, similar hypertension is easily produced in animals by acute constriction of the aorta. Barcroft,[2,3] Brotchner[4] and Page[5] have shown that after acute aortic constriction in dogs there is an immediate elevation of the blood pressure which is proportional to the amount of obstruction to the blood flow. Assuming for the moment that the hypertension of aortic coarctation is similarly based entirely upon mechanical grounds, it is pertinent to inquire into the compensatory changes which might occur as a result of the hypertension. As Lewis[6] pointed out, one would expect the carotid sinus (and aortic) reflexes to become active, slowing the pulse, decreasing peripheral resistance, increasing peripheral blood flow and tending to decrease the blood pressure. Bradycardia, however, is not a feature of aortic coarctation as it is in experimental animals with acute constriction of the aorta.[5] Clinical evidence suggests that vasodilation and increased blood flow occur in the area above the coarctation[6] (warm hands, high facial coloring and capillary pulsations) but it is to be noted that the presence of warm or flushed skin is not necessarily indicative of increased total blood flow to that extremity.[7,8] Laboratory investigations of peripheral blood flow have yielded inconclusive results. Blumgart[9] found normal arteriolar pressures in the arms which was interpreted as signifying increased resistance between the aorta and the point measured. Increased cerebral blood flow with increased cerebral oxygen consumption but normal cerebral vascular resistance has recently been found in two patients with coarctation.[10] Decreased blood flow through the upper extremities has been found by Prinzmetal and Wilson,[11] normal blood flow by Pickering,[12] Lewis[6] and Wakim et al.,[13] and finally increased blood flow by Bing et al.[14] This divergence of opinion probably indicates inadequate methods; at any rate there is no conclusive evidence of a marked shift of blood flow from the normal. Since the mean brachial pressure is usually elevated, resistance to blood flow is probably increased. Both Prinzmetal and Wilson[11] and Woodbury[15] have shown that

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reflex action and drugs can decrease the high resistance and increase the blood flow even in collateral circulation. Reflex response to the hypertension is therefore not limited by an inability of the vessels to react. Similarly, the cardiac output is not depressed but is essentially normal or even elevated in the presence of the hypertension.[14,16,17] One is therefore forced to conclude that a simple mechanical explanation for the hypertension above the constriction is inadequate. Although it may be true that mechanical obstruction may initiate the hypertension, some other mechanism appears either to contribute to that hypertension by increasing peripheral resistance or, at least, to prevent the full action of compensatory mechanisms designed to lower the blood pressure.*

The second portion of the discussion concerns the pressure relationships below the constricted area and the entrance of the collaterals. By cuff measurements the blood pressure is markedly diminished or seemingly absent in the lower extremities.† However, Steele[1] was able to demonstrate normal to elevated diastolic pressure and normal to low systolic pressures in the femoral artery by direct measurements with the Hamilton manometer. These observations have been amply confirmed[14,15,19,20] but there is some variation in the observed values which are tabulated in Table I. The values obtained by us in five patients are shown in Table II. As a rule the diastolic pressure is elevated in coarctation, the systolic pressure is within normal limits and the mean pressure ranges from low normal to high.

Part of these changes may be explained on a mechanical basis. Hull[18] has pointed out that partial occlusion of the brachial artery will cause an elevation of the diastolic pressure and a fall of the systolic pressure distal to the occlusion. Wilkins and Bradley[21] have even demonstrated an increase in mean pressure in similar experiments, possibly arising because the partial occlusion acts as a check valve and prevents regurgitation during the diastolic phase.

A complete interpretation of the changes in pressure, particularly the mean pressure, depends upon whether the total rate of blood flow through the constriction and collaterals is normal or diminished. No direct measurements of this quantity can be made. Indirect measurements as by estimates of the kidney or leg circulation are unsatisfactory, inconclusive and variable. Lewis[6] found normal blood flows through the leg and confirmed this observation by the clinical finding that intermittent claudication is rare. Blumgart[9] observed normal arteriovenous oxygen differences in the lower extremity and again pointed out that intermittent claudication occurs only with heart failure. Normal leg blood flows were also found by the Mayo group.[13] Bing[14] differs in finding markedly low leg blood flows and Hull[18] notes that cold feet, numbness and pallor of the feet and intermittent claudication point to diminished leg blood flow. (As previously mentioned, the state of the skin does not, however, indicate the total blood flow to an extremity.) On the other hand, many of the male patients, as the patient in Case III, can indulge in such vigorous activity as to preclude any diminution in blood flow to the muscles.

Since the total blood flow through the area beneath the coarctation cannot be measured, the question of increased resistance in this area cannot be answered definitely. There are several indirect evi-

* After this paper was submitted for publication, our attention was called to the work of Goldman and Schroeder (Coarctation of the aorta. *Am. J. Med.*, 7: 454, 1949) who studied the hemodynamics of patients with aortic coarctation by means of photoelectric plethysmography and direct arterial blood pressures. They found a relatively low magnitude of the pulse, similar to that seen in generalized hypertension, in the upper extremities of four patients. On the other hand, increased amplitude was noted in eight cases, evidence for a mechanical factor being present. The authors concluded from this and a study of direct arterial pressures that both humoral and mechanical factors may operate to elevate the blood pressure in patients with aortic coarctation.

† Failure to observe the correct pressure by ordinary means is probably related to the very low pulse pressure caused by damping of the pulse by the resistance of the constriction and the asynchronous filling of the vessels through the collaterals.[4,6,18]

TABLE I

DIRECT BLOOD PRESSURES IN AORTIC COARCTATION

Author	Cases	Brachial			Femoral		
		Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
Steele et al.[1]	Coarctation	201	128	159*	134	120	126*
	Coarctation	250	132	183*	120	90	103*
	Coarctation	195	110	146*	126	108	116*
Woodbury et al.[15]	Coarctation	160	88	113	105	82	93
Brown et al.[20]	Six normal	130 (122–142)	68 (65–70)	95*	127 (120–134)	64 (58–69)	91*
	Coarctation (25 cases)	194 (161–230)	96 (76–126)	138*	113 (87–143)	81 (63–104)	95*
	End-to-end resection (8 cases preoperative)	200 (169–226)	103 (84–126)	145*	115 (93–143)	83 (70–104)	97*
	(8 cases postoperative)	171 (136–236)	84 (71–94)	121*	135 (117–166)	78 (63–91)	102*
	Subclavian anastomosis (3 cases preoperative)	184 (172–204)	94 (80–107)	133*	103 (87–122)	74 (63–88)	86*
	(3 cases postoperative)	182 (161–209)	80 (78–82)	124*	106 (94–116)	66 (60–72)	83*
Brown et al.[19]	(Preoperative)	169	126	144*	108	92	99*
	(Postoperative)	147	75	106*	117	63	86*
Bing et al.[14]	(17 cases preoperative)	183 (205–133)	106 (38–134)	144 (98–174)	91 (52–125)	68 (45–98)	81 (48–103)
	(12 cases postoperative)	141 (112–178)	85 (65–140)	109 (88–147)	128 (89–178)	78 (58–102)	100 (78–140)

* Mean pressure calculated as diastolic pressure plus 43 per cent of pulse pressure. Figures in parentheses indicate range of pressure.

TABLE II

BLOOD PRESSURES IN PATIENTS WITH COARCTATION OF THE AORTA AS MEASURED WITH THE HAMILTON MANOMETER

Case	Age (yr.)	Sex	Preoperative Pressures						Pressures 1 to 2 Weeks Postoperatively					
			Brachial			Femoral			Brachial			Femoral		
			Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean	Systolic	Diastolic	Mean
H. T.	30	M	175	82	113	92	70	80	169	74	106	112	75	90
C. G.	15	F	192	112	145	114	89	102	154	98	122	153	99	102
E. W.	21	F	174	96	126	114	95	103	154	87	112	118	84	99
R. C.	18	M	191	106	141	133	98	117	150	77	103	108	79	96
V. P.	21	M	168	90	120	100	77	89	200	96	131	117	86	101
Average:			180	97.2	129	110.6	85.8	98.2	165.4	86.4	114.8	121.6	84.6	97.6

dences that resistance is not low beneath the area of constriction. In human cases of coarctation the mean pressure may be elevated above normal in the femoral artery. If this were definite and significant, beyond that due to prevention of regurgitation (*vide supra*), there must be either supranormal blood flow to the area or increased total resistance beneath the coarctation and collaterals. The former is unlikely and, if present, would require explanation as to why the pressure above the constriction is great enough to give increased blood flow below. The latter, increased resistance peripheral to the constriction, would be the only logical explanation of an unequivocally increased mean femoral pressure. Some cases show this increased mean pressure (the patient in Case III and those in Brown's series[20] with diastolic pressures higher than the normal mean pressures). Unfortunately in humans, with one exception, one cannot determine whether ordinary essential hypertension is a complication or whether there are associated congenital anomalies such as a congenitally hypoplastic aorta and tributaries. If, however, the mean femoral pressure should fall postoperatively as it did in Case III and in Brown's case,[19] increased resistance must have existed prior to operation unless the operation further decreased the blood flow through the constriction and collaterals. That this did not occur in the aforementioned cases is indicated by the drop in brachial mean pressures.

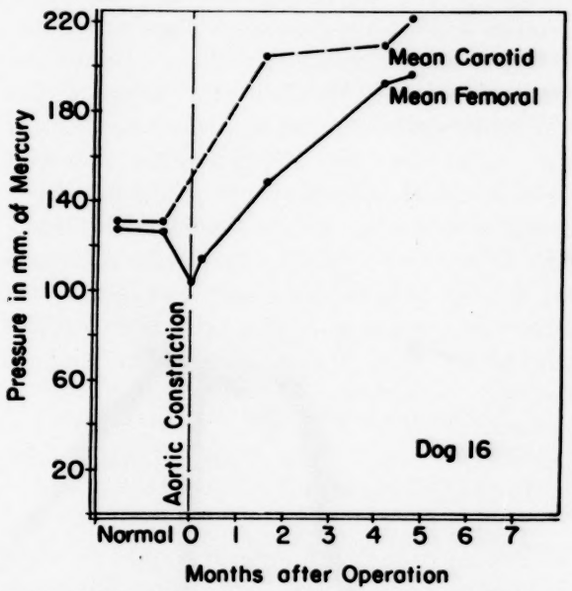

FIG. 1. Mean arterial pressures following experimental aortic coarctation.

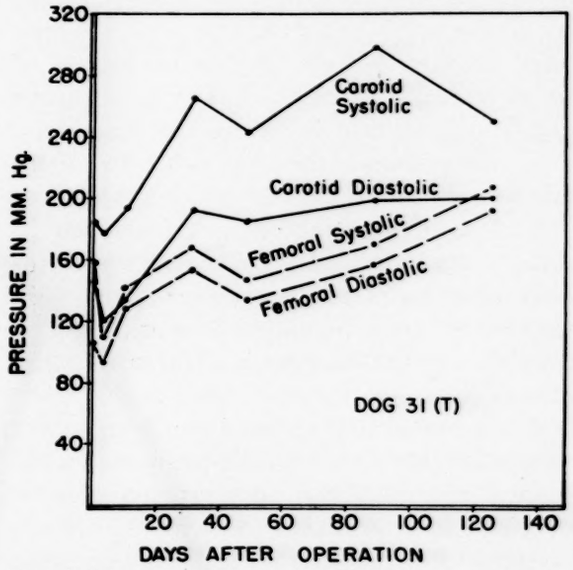

FIG. 2. Direct arterial pressures following experimental aortic coarctation.

Conclusive evidence against a purely mechanical theory can be obtained from animal experiments. Dogs in which artificial coarctation of the thoracic aorta has been produced[22] show an immediate fall in mean femoral arterial pressure which then rises above normal and continues to rise slowly to unquestionably markedly elevated levels.[23,24] The pressures of two such dogs are shown in Figures 1 and 2. Several points in these curves are pertinent to the present discussion. The pressures in the carotids, which are elevated above normal at the first postoperative measurement, continue to increase for several months.* The femoral pressures, which are very low immediately after the operation, rise until systolic, diastolic and mean pressures are markedly increased. According to a purely mechanical theory, the height of the carotid pressures should be

* Autopsies on several dogs have shown the aorta to be patent, without thrombi. Thrombus formation, although it might explain increasing pressures above the coarctation, could not explain the increasing pressures below the constriction.

reached shortly after the operation and should decrease thereafter as collateral circulation improves. The femoral mean pressure should rise slowly as the collateral circulation improves and should asymptotically reach the original normal levels as the collateral circulation becomes equivalent to the original aorta. The actual events differ markedly from the implications of the mechanical theory. Thus evidence from human coarctation indicates the deficiency of a mechanical theory; evidence from animals refutes it. In the lower extremities as well as the upper extremities, both in humans and animals, some other mechanism must contribute to the changes in vascular dynamics which follow and may be initiated by the mechanical factors of the obstruction.

When Steele first showed the presence of normal or elevated diastolic pressures in the femoral arteries,[25] he postulated a general increase in arteriolar tone which he compared to that in essential hypertension and ascribed to the effects of renal ischemia (the coarctation acting as a Goldblatt clamp).

In acute animal experiments Steele[26] showed that constriction of the aorta above the renal arteries of dogs leads to a rise in pressure above the constriction and sometimes, after a period of five days, to supranormal femoral diastolic pressures. Confirmatory evidence was furnished by Rytand and others.[5,27–29] Rytand showed that constriction of the aorta above the kidneys in rats gave rise to cardiac hypertrophy. This hypertrophy was also evident if the aorta was constricted between the origins of the renal arteries but not if the lower kidney were removed. Page[5] demonstrated acute hypertension in dogs above a sudden occlusion of the aortic arch. This acute rise could not be prevented by removal of the kidneys or adrenals nor by pithing and was presumably on a mechanical basis. A similar hypertension was not produced by constricting the aorta at the arch or at the proximal descending portion, but clamping below the kidneys followed by a clamp low in the thoracic aorta resulted in hypertension after an interval of time. From these acute experiments (longest duration was twenty days) Page concluded that hypertension in human coarctation was of renal origin. Goldblatt, Kahn and Hanzal[29] supported this hypothesis by showing that clamping the aorta just above the renal arteries led to hypertension above the constriction and sometimes to later rises of the femoral pressure to above the preoperative levels. When the aorta was clamped below the renal arteries, hypertension was not produced. However, they could not successfully constrict the thoracic aorta. Page did so but was unable to produce hypertension by this means alone and stated, "It does not appear that the complete clinical picture of coarctation similar to that in human beings has been reproduced in animals."[5] The results in these older experiments are not, therefore, strictly analogous to human coarctation.

Additional evidence for the presence of a kidney mechanism has been sought in cases of human coarctation. This work is largely based upon attempts to show a generalized increase in peripheral resistance similar to that obtaining in experimental renal or human essential hypertension. As we have demonstrated, critical evaluation of this type of evidence does not permit definite conclusions. Even those who agree on the elevation of peripheral resistance in the upper extremities differ on the mechanism of the increase. Prinzmetal and Wilson[11] observed a low rate of blood flow which responded in supranormal fashion to dilatation by heat. They concluded that the increase of resistance was on a vasomotor nerve basis, acting as compensatory mechanism to maintain normal distribution of blood. In support Graybiel et al.[30] were unable to find histologic evidence of any organic change in either the upper or lower extremities. On the other hand, Pickering[12] came to the opposite conclusion that the increase in resistance was due to vascular narrowing not neuronally induced.

This type of evidence was recently summarized and amplified by Bing et al.[14]

These investigators found normal resistance in the upper extremities and increased resistance in the lower extremities as determined by direct arterial pressures and measurements of the blood flow through the forearm and calf. Calculations showed that the total peripheral resistance was low. They concluded that the low total peripheral resistance in presence of normal or high resistance in the extremities indicated an area of quite low vascular resistance and that the unequal distribution of blood excluded a renal origin for the hypertension. However, analysis of their calculations does not bear out their conclusions. They determined maximal peripheral resistance by the formula

$$RP = R_t - rc$$

When RP is the total resistance of the peripheral arterioles, R_t is the total over-all resistance and rc is the resistance through the collaterals and the coarctation.

Since they assumed a minimal resistance for rc by using the formula

$$rc = P_c/\text{cardiac output}$$

they believed that their calculation of the peripheral resistance would represent the highest possible value. (P_c is the loss in mean pressure head across the coarctation and the collaterals.) However, the resistance of the collaterals cannot be directly subtracted from the total over-all resistance since it is in series with part of that resistance (the resistance below the coarctation) and in parallel with the remainder (resistance above the collaterals and coarctation). A closer approximation to the correct formula would be

$$1/R_t = 1/R_u + 1/(R_1 + rc)$$

when R_u equals the peripheral resistance above the coarctation and collaterals, and R_1 equals the peripheral resistance below the coarctation and collaterals.

This equation contains too many unknowns for calculation but estimates of the total peripheral resistance may be made by assuming various fractions (from 10 to 90 per cent) of the cardiac output to be the blood flow to the area below the coarctation. Then

$$R_u = P_u/F_u$$
$$R_1 = P_1/F_1$$
$$rc = P_c/F_1$$

When P_u is the mean arterial pressure above the coarctation, P_1 is the mean pressure below the coarctation, F_u is the blood flow to the area above the coarctation, F_1 is the blood flow to the area below the coarctation and

$$RP = 1/R_u + 1/R_1$$

When this is done, using the data of Bing et al.[14] it is found that the values for peripheral resistance are higher than their calculated ones at any assumed division of the cardiac output to the areas above and below the coarctation. Their estimated values for peripheral resistance are actually minimal rather than maximal.

Because of the evidence indicating inadequacy of the mechanical theory and because of the lack of direct evidence implicating the kidneys, we wished to investigate further the relationship between the hypertension and the kidneys by observation of the changes in renal dynamics before and at intervals following surgical relief of the coarctation.

METHODS

Direct pressures were measured by intra-arterial puncture with Cournand needles and recorded optically with the Hamilton manometer. Mean pressures were determined by planimetric integration covering a period of at least two respiratory cycles.*

The renal studies were performed as recommended by the New York University Group.[31] All clearances were determined in the morning under basal conditions. Prior to the day of examination the nature of the tests and their purpose were discussed in detail so that the actual procedure would not cause apprehension which would interfere with the renal dynamics. Diuresis was obtained with water orally and the drugs were given intravenously as priming solu-

* We are indebted to Dr. J. D. Myers for these determinations.

tions followed with constant drip infusions. After each period the bladder was washed three times with a total of 40 to 50 cc. of sterile distilled water. A minimum of three clearance periods of fifteen to twenty minutes each was used to obtain the average figures.

The average determinations were then corrected to a body surface area of 1.73 sq. M. Effective renal plasma flow and total excretory mass were measured by means of sodium para amino hippurate and glomerular filtration rates by inulin clearances.

Relatively constant plasma levels of 30 to 40 mg. per cent inulin were maintained for the determination of glomerular filtration rate. The corresponding levels for effective renal plasma flow were 1 to 3 mg. per cent and for total excretory mass were 50 to 80 mg. per cent amino hippurate. Chemical determinations were slightly modified from the methods of Goldring and Chasis[31] using an alcoholic diphenylamine reagent for inulin.[32]

Four patients were examined by these methods shortly before operation, five to seven days postoperatively and again two to four months after operation.

Case I. C. G., a fifteen year old white female, entered Duke Hospital because of weight loss and severe frontal headaches lately associated with nausea and vomiting. The patient always "tired easily in the legs." She had never menstruated nor shown evidence of puberty. Physical examination revealed a short, stocky girl with underdeveloped breasts, absent axillary hair and scant pubic hair. The brachial blood pressure was 180/100 and the femoral pressure 100/90 by cuff measurements. The suprascapular arteries were palpable but the arteries in the lower extremities were not. The heart was enlarged and the typical systolic murmur was heard. There was a definite narrowing of the arterioles of the optic fundi. The uterus and ovaries were not palpable on rectal examination. X-rays showed the cardiac enlargement and notching of the ribs. The electrocardiogram was essentially normal as were routine blood and urine studies. Urinary gonadotrophins were within normal limits. The clinical impression was coarctation of the aorta and Turner's syndrome (eugonadotrophic apubescence with statural retardation). (The occurrence of ovarian insufficiency and decreased stature in aortic coarctation has been summarized by Goldman et al.[33] who found five instances in the literature and added four cases of their own.) Operation was performed on June 8, 1948, and an end-to-end anastomosis of the aorta was performed after the coarcted area was resected. The aorta showed a stenotic segment (orifice of 3 to 4 mm. diameter) 2 cm. below the origin of the left subclavian. No hypoplasia of the aorta was noted. The postoperative course was uneventful.

Case II. E. W., a twenty-one year old white female, was known to have aortic coarctation since the age of seven years. She had no complaints except for occasional headaches and minimal dyspnea on effort. Physical examination revealed the characteristic evidence of aortic coarctation, brachial blood pressure of 170/95, femoral blood pressure of 109/96, palpable collateral vessels in the suprascapular region, precordial systolic murmur and absent pulsations in the popliteals, posterior tibial and dorsalis pedis arteries. Laboratory data were not remarkable.

Operation was performed on June 28, 1948. Excellent collateral circulation was noted. The coarctation was 2.5 cm. below the left subclavian orifice and just below the attachment of the ligamentum arteriosum. A resection and end-to-end anastomosis of the aorta was made. The orifice of the coarctation was 2 to 3 mm. in diameter. The postoperative course was uneventful.

Case III. R. C., an eighteen year old white male, had always enjoyed excellent health except for the complaint of cold feet. In spite of this he was very active in sports, excelling in football, baseball, track and boxing. On very prolonged and strenuous exertion he occasionally developed headache, scotomas, transient giddiness and minimal cramping in the calves. Hypertension was discovered after enlistment in the army and later a diagnosis of coarctation was made. Physical examination revealed a muscular, well developed, athletic male. There was no obvious evidence of collateral circulation but x-rays revealed the characteristic rib erosions. The heart was not enlarged but the usual systolic murmur was present. Pulsations were not palpable in the abdominal aorta or in any of the more distal vessels. The electrocardiogram was not remarkable. Brachial blood pressure was 175/99; the femoral pressure could not be obtained. Operation was performed on October 4, 1948. A stricture of the aorta was found 4.5 cm. distal to the origin of the left subclavian at the

junction of the ligamentum arteriosum. From the left subclavian to the stricture the aorta was hypoplastic, about the same size as the left subclavian artery. Below the stricture the aorta was somewhat widened. The stricture was excised and end-to-end anastomosis of the aorta performed. The postoperative course was uneventful. The coarctation had an internal diameter of less than 1 mm.

CASE IV. V. P., a twenty-one year old white male, had complained for many years of spells of nervousness, weak stomach, palpitations, light-headedness, rapid respirations and sweating of the palms. These spells were unrelated to exertion and were partially relieved by eructation and urination. Four years before he was rejected by the navy because of hypertension. Since then his nervous spells had become more severe. On questioning he stated that he had noted cold feet but no pain on exertion. Physical examination revealed a tall, well developed, apprehensive male. Cuff pressures in the arms were 174/98. The pressures could not be measured in the lower extremities. The femoral pulsations were weak and the pulsations in the popliteal and pedal arteries could not be felt. X-rays showed slight cardiac enlargement and notching of the ribs. The electrocardiogram was normal.

Operation was performed on January 14, 1949. The aorta was found to be markedly hypoplastic from the origin of the left subclavian to the junction of the ligamentum arteriosum (about 5 cm.). The left subclavian was freed and divided. The stricture was excised and shown to have no lumen; 1 cm. of the hypoplastic aorta was also excised and the left subclavian was anastomosed to the descending aorta. The postoperative course was uneventful. Following operation pulsations could be felt in the femoral and posterior tibial arteries but not in the anterior tibials. There was marked relief of the nervous spells.

RESULTS

The pertinent data for Cases I, II and III are shown in Tables III, IV and V. In these cases the preoperative glomerular filtration rates, effective renal plasma and blood flows were low to normal. The filtration fractions were normal. The tubular excretory masses were normal in two cases and somewhat high in the third.

In the early postoperative period, approximately one week after operation, all cases showed rises in glomerular filtration rates amounting to 33, 21 and 31 per cent of the original value. The effective renal plasma flows likewise rose (13, 24 and 24 per cent) as did the effective renal blood flows (8, 32 and 13 per cent). The filtration fractions were either unchanged or rose slightly.

On retesting from two to four months after operation it was found that these values had largely reverted to their preoperative levels. The tubular excretory mass was remeasured in Case I and was essentially the same as prior to operation. An attempt was made to remeasure the excretory mass in Case II but was discontinued because of a severe reaction. Thereafter the tubular excretory mass was determined preoperatively only since it was normal in all the cases and since it was not considered sufficiently informative to risk an equally severe reaction in the postoperative period.

The changes in renal dynamics did not parallel the changes in blood pressure. All three patients showed a fall in brachial mean pressure during the early postoperative period when the filtration rates and effective renal plasma and blood flows were increasing. At this point it might appear that the blood pressure was directly related to the renal dynamics and that the renal origin for the hypertension might be assumed. However, the brachial mean pressure continued to fall in the next few months. In spite of this the renal rates showed a reversion to preoperative levels. The filtration fractions were only slightly changed, being somewhat higher postoperatively rather than lower as might be expected. There was also no correlation between the renal dynamics and the femoral mean or pulse pressure. The first patient showed a rise in femoral mean pressure, the second showed no change and the third showed a fall. Two patients showed a rise in femoral pulse pressure but the third showed no change. The changes in renal

TABLE III

COARCTATION OF THE AORTA—CASE I, C. G., TURNER'S SYNDROME

Renal Data

Date	Days Postoperatively	Glomerular Filtration Rate	Renal Plasma Flow	Filtration Fraction	Renal Blood Flow	Tm
5/20/48	..	94	472	0.20	773	80
6/16/48	7	125	534	0.23	833	..
9/4/48	87	100	452	0.22	755	74

Blood Pressure

Date	Days Postoperatively	Brachial				Femoral			
		Mean	Pulse	Systolic	Diastolic	Mean	Pulse	Systolic	Diastolic
5/22/48	....	145	80	192	112	102	25	114	89
6/21/48	12	122	56	154	98	121	54	153	99
9/4/48	87*	105	50	134	84	122	42	146	104
12/13/48	187*	108	56	140	84	99	54	130	76

* Cuff pressures.

TABLE IV

COARCTATION OF THE AORTA—CASE II

Renal Data

Date	Days Postoperatively	Glomerular Filtration Rate	Renal Plasma Flow	Filtration Fraction	Renal Blood Flow	Tm
6/19/48	...	124	650	0.19	1002	67
6/29/48	8	150	805	0.19	1320	..
10/11/48	112	124	629	0.20	1086	..

Blood Pressure

Date	Days Postoperatively	Brachial				Femoral			
		Mean	Pulse	Systolic	Diastolic	Mean	Pulse	Systolic	Diastolic
6/14/48	....	126	78	174	96	103	19	114	95
7/2/48	11	112	67	154	87	99	34	118	84
10/11/48	112*	100	70	140	70	103	30	120	90
11/8/48	140*	100	70	140	70	103	30	120	90

* Cuff pressures.

TABLE V

COARCTATION OF THE AORTA—CASE III

Renal Data

Date	Days Postoperatively	Glomerular Filtration Rate	Renal Plasma Flow	Filtration Fraction	Renal Blood Flow	Tm
9/30/48	..	103	530	0.19	957	96
10/15/48	11	135	658	0.21	1080	..
12/3/48	60	114	527	0.22	985	..

Blood Pressure

Date	Days Postoperatively	Brachial				Femoral			
		Mean	Pulse	Systolic	Diastolic	Mean	Pulse	Systolic	Diastolic
9/30/48	..	141	85	191	106	117	35	133	98
10/19/48	15	103	73	150	77	96	29	108	79
12/3/48	60	91	70	139	69	95	38	115	77
1/11/49	99*	98	66	136	70	110	28	126	98

* Cuff pressures.

TABLE VI

COARCTATION OF THE AORTA—CASE IV, V. P.

Renal Data

Date	Days Postoperatively	Glomerular Filtration Rate	Renal Plasma Flow	Filtration Fraction	Renal Blood Flow	Tm
1/12/49	..	122	406	0.30	790	80.4
1/25/49	13	136	493	0.28	900	....
3/35/49	72	117	475	0.25	896	....

Blood Pressure

Date	Days Postoperatively		Brachial				Femoral			
			Mean	Pulse	Systolic	Diastolic	Mean	Pulse	Systolic	Diastolic
1/12/49	..		120	78	168	90	89	23	100	77
1/25/49	13		131	104	200	96	101	31	117	86
3/22/49	69		117	81	167	86	92	22	104	82
5/20/49*	128	Left	89	16	98	82	101	10	107	97
		Right	121	110	184	74				

* Cuff pressures.

dynamics were nevertheless quite similar in all cases.

The fourth case is instructive in a negative sense. (Table VI.) Preoperatively this patient showed a normal glomerular filtration rate, low renal plasma flow and elevated filtration fraction, a picture resembling early essential hypertension.[34] After operation the renal plasma flow rose and the filtration fraction dropped. The rise in renal plasma flow was largely maintained two and a half months after operation and the filtration fraction continued to fall. However, this patient showed no benefit from the operation as determined by direct blood pressures. Neither brachial nor femoral pressure values were altered postoperatively. In this case the aorta was hypoplastic and the left subclavian was anastomosed to the distal aorta.* Although the changes in renal dynamics might indicate improvement postoperatively, they have no relation to the blood pressure in this case. The renal findings are better correlated with the patient's neurotic apprehension since apprehension will cause similar changes in a normal individual.[35] As the patient became more familiar with the test, his apprehension diminished and his renal plasma flow increased with decrease in the filtration fraction. In support of this it will be noted that the tubular excretory mass was normal preoperatively.

COMMENTS

The preoperative findings in our cases do not agree with those of Friedman et al.[36] who found normal glomerular filtration rates, low renal blood flows and elevated filtration fractions in six patients. While this work was in progress, Genest and his co-workers reported their findings in seventeen patients, twelve of whom were reexamined three weeks postoperatively.[37] After operation the renal filtration rate increased in five patients, decreased in two and remained unchanged in five cases. The effective renal blood flow increased in seven, decreased in one and remained unchanged in four patients. The filtration fraction increased in four, decreased in six and was unchanged in two. We have found rises in glomerular filtration rate and renal blood flow in the immediate postoperative period which revert toward preoperative levels in the succeeding months. Perhaps some of the variations in the results and the average increases in these values found by Genest and his co-workers may result from the time at which the determinations were made. Repeated tests done after several months might show, as ours have, a reversion toward preoperative levels. At any rate, Genest was unable to determine the relationship between the renal blood flow and the blood pressure. Spot graphs of the changes in blood pressure against the changes in either filtration fraction, glomerular filtration rate or renal blood flow do not show any correlation between these variables.

The failure to correlate hypertension with changes in renal blood flow makes it impossible to ascribe the etiology of the hypertension to renal ischemia. However, there is considerable disagreement as to whether renal ischemia *per se* is the initiating factor in experimental renal hypertension.[38,39] For example, Corcoran and Page[40] have found that the renal dynamics may be normal in dogs made hypertensive by renal artery constriction or perinephritis. It has been demonstrated that the blood flow may return to normal after renal artery constriction[41] and that the arterial pressure distal to constriction of renal artery in dogs bears no direct relation to the level of the systemic blood pressure.[42] For these reasons, among others, it has been suggested that the stimulus to production of renin is related to the pulse pressure rather than to renal ischemia or a fall in renal artery pressure.[43–45] Through such a mechanism the kidney could produce hypertension in coarctation of the aorta since the pulse pressure in the distal aorta is characteristically low. However, the presence of hypertension in cases in which the coarcta-

* Measurements of brachial pressure were made on the right arm.

tion is below the level of the renal arteries would eliminate even this possibility if the aorta were not hypoplastic proximal to that point.[46]

Our data suggest that the changes in renal dynamics play a secondary rather than a primary role in the alterations in blood pressure. The tendency for the filtration rate and renal plasma flow to be low indicates a functionally small kidney, perhaps as a result of the long-standing changes in blood pressure or on a congenital basis similar to the frequent coexistence of Turner's syndrome as in Case I. The rise and later fall in filtration and blood flow seem to be compensatory to the operation and the resulting changes in blood pressure. The kidney, however, soon adjusts its intrarenal dynamics to the new conditions and returns to the preoperative state.

Both Friedman[36] and Genest[37] and their co-workers have likened the renal pattern which they found in aortic coarctation to that noted by Goldring et al.[34] in essential hypertension. However, neither group measured the total excretory mass which is decreased in established essential hypertension.[31] We have found that the total excretory mass is not subnormal in our patients who have had hypertension for a considerable period of time. In addition the filtration fractions in three of our patients were not elevated. This was also true in five of the seventeen cases reported by Genest et al.[37] Of greater significance is the fact that the filtration fraction did not fall postoperatively in three of our cases or in one-half of the cases reported by Genest. These results indicate that the increased filtration fraction found in some of their cases was not intimately associated with the increased blood pressure as it is in cases of essential hypertension.

SUMMARY

Examination of the changes in blood pressure in both human and experimental aortic coarctation indicates that these alterations cannot be explained solely as a result of the mechanical effects of the lesion. Studies of the renal dynamics before and after operation in human coarctation fail to show a correlation with the blood pressure changes. It is concluded that other mechanisms, besides the increased resistance imposed by the constriction and collaterals, are necessary to explain the hypertension of aortic coarctation. These mechanisms apparently do not involve renal ischemia.

REFERENCES

1. Steele, J. M. Evidence for general distribution of peripheral resistance in coarctation of the aorta: report of three cases. *J. Clin. Investigation*, 20: 473, 1941.
2. Barcroft, H. Cardiac output and blood distribution. *J. Physiol.*, 71: 280, 1931.
3. Barcroft, H. and Formijne, P. The relation of the central nervous system to the increase in systemic flow produced by occlusion of the thoracic aorta. *J. Physiol.*, 82: 377, 1934.
4. Brotchner, R. J. Etiology of hypertension resulting from coarctation of the aorta. *Arch. Path.*, 28: 676, 1939.
5. Page, I. H. The effect of chronic constriction of the aorta on arterial blood pressure in dogs: an attempt to produce coarctation of the aorta. *Am. Heart J.*, 19: 218, 1940.
6. Lewis, T. Material relating to coarctation of the aorta of the adult type. *Heart*, 16: 205, 1933.
7. Kunkel, P., Stead, E. A., Jr. and Weiss, S. Blood flow and vasomotor reactions in the hand, forearm, foot and calf in response to physical and chemical stimuli. *J. Clin. Investigation*, 18: 225, 1939.
8. Barcroft, H., Edholm, O. G., McMichael, J. and Sharpey-Schafer, E. P. Posthaemorrhagic fainting, study by cardiac output and forearm flow. *Lancet*, 246: 489, 1944.
9. Blumgart, H. L., Lawrence, J. S. and Ernstene, A. C. The dynamics of the circulation in coarctation (stenosis of the isthmus) of the aorta of the adult type. Relation to essential hypertension. *Arch. Int. Med.*, 47: 806, 1931.
10. Hafkenschiel, J. H., Jr., Crumpton, C. W. and Moyer, J. H. Blood flow and oxygen consumption of the brain in coarctation of the aorta. *Proc. Soc. Exper. Biol. & Med.*, 71: 165, 1949.
11. Prinzmetal, M. and Wilson, C. The nature of the peripheral resistance in arterial hypertension with special reference to the vasomotor system. *J. Clin. Investigation*, 15: 63, 1936.
12. Pickering, G. W. The peripheral resistance in persistent arterial hypertension. *Clin. Sc.* 2: 209, 1936.
13. Wakim, K. G., Slaughter, O. and Clagett, O. T. Studies on the blood flow in the extremities in cases of coarctation of the aorta. Determinations before and after excision of the coarctate region. *Proc. Staff Meet., Mayo Clin.*, 23: 347, 1948.
14. Bing, R. J., Handelsman, J. C., Campbell, J. A., Griswold, H. E. and Blalock, A. The surgical

treatment and the physiopathology of coarctation of the aorta. *Ann. Surg.*, 128: 803, 1948.

15. Woodbury, R. A., Murphey, E. E. and Hamilton, W. F. Blood pressures in aortic coarctation. Study of pulse contours taken by the direct method. *Arch. Int. Med.*, 65: 752, 1940.
16. Grollman, A. and Ferrigan, J. P., Jr. Cardiac output: its related functions in a case of coarctation of the aorta. *Arch. Int. Med.*, 53: 35, 1934.
17. Stewart, H. J. and Bailey, R. L., Jr. The cardiac output and other measurements of the circulation in coarctation of the aorta. *J. Clin. Investigation*, 20: 145, 1941.
18. Hull, E. On the evidence for generalized arteriolar constriction in coarctation of the aorta. *Am. Heart J.*, 35: 980, 1948.
19. Brown, G. E., Jr., Pollock, A. H., Clagett, O. T. and Wood, E. H. Intra-arterial blood pressure in patients with coarctation of the aorta. *Proc. Staff Meet., Mayo Clin.*, 23: 129, 1948.
20. Brown, G. E., Jr., Clagett, O. T., Burchell, H. B. and Wood, E. H. Preoperative and postoperative studies of intraradial and intrafemoral pressures in patients with coarctation of the aorta. *Proc. Staff Meet., Mayo Clin.*, 23: 352, 1948.
21. Wilkins, R. W. and Bradley, S. E. Changes in arterial and venous blood pressure and flow distal to a cuff inflated on the human arm. *Am. J. Physiol.*, 147: 260, 1946.
22. Sealy, W. C. and McSwain, G. H. A method for producing coarctation of the thoracic aorta in dogs. *Surgery*, 25: 451, 1949.
23. Sealy, W. C. Arterial hypertension produced by experimental stenosis of the thoracic aorta. *Proc. Soc. Exper. Biol. & Med.*, 71: 174, 1949.
24. Sealy, W. C., DeMaria, W. and Harris, J. S. Studies on the development and nature of the hypertension in experimental coarctation of the aorta. *Surg., Gynec. & Obst.*, 90: 193, 1950.
25. Steele, J. M. and Cohn, A. E. The nature of hypertension in coarctation of the aorta. *J. Clin. Investigation*, 17: 514, 1938.
26. Steele, J. M. Effect of partial clamping of aorta in dogs upon diastolic pressure in carotid and femoral arteries. *Proc. Soc. Exper. Biol. & Med.*, 41: 86, 1939.
27. Rytand, D. A. Pathogenesis of arterial hypertension in coarctation of the aorta. *Proc. Soc. Exper. Biol. & Med.*, 38: 10, 1938.
28. Rytand, D. A. The renal factor in arterial hypertension with coarctation of the aorta. *J. Clin. Investigation*, 17: 391, 1938.
29. Goldblatt, H., Kahn, J. R. and Hanzal, R. F. Studies on experimental hypertension. ix. The effect on blood pressure of constriction of the abdominal aorta above and below the site of origin of both main renal arteries. *J. Exper. Med.*, 69: 649, 1939.
30. Graybiel, A., Allen, A. W. and White, P. D. A histological study of the arterioles of the muscle and skin from the arm and leg in individuals with coarctation of the aorta. *J. Clin. Investigation*, 14: 52, 1935.
31. Goldring, W. and Chasis, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
32. Alving, A. S., Rubin, J. and Miller, B. F. A direct colorimetric method for determination of inulin in blood and urine. *J. Biol. Chem.* 127: 609, 1939.
33. Goldman, M. L., Schroeder, H. A. and Futcher, P. H. Coarctation of the aorta associated with abnormal digits, ovarian insufficiency and shortness of stature. *J. Clin. Endocrinol.*, 9: 622, 1949.
34. Goldring, W., Chasis, H., Ranges, H. A. and Smith, H. W. Effective renal blood flow in subjects with essential hypertension. *J. Clin. Investigation*, 20: 637, 1941.
35. Smith, H. W. Physiology of the renal circulation. *Harvey Lect.*, 35: 167, 1940.
36. Friedman, M., Selzer, A. and Rosenblum, H. The renal blood flow in coarctation of the aorta. *J. Clin. Investigation*, 20: 107, 1941.
37. Genest, J., Newman, E. V., Kattus, A. A., Sinclair-Smith B. and Genecin, A. Renal function before and after surgical resection of coarctation of the aorta. *Bull. Johns Hopkins Hosp.*, 83: 429, 1948.
38. Experimental Hypertension. Vol. iii. New York, 1946. Special Publications of the New York Academy of Sciences.
39. Corcoran, A. C. and Page, I. H. Renal aspects of experimental and clinical hypertension. *J. Lab. & Clin. Med.*, 26: 1713, 1941.
40. Corcoran, A. C. and Page, I. H. Renal blood flow in experimental renal hypertension. *Am. J. Physiol.*, 135: 361, 1942.
41. Schroeder, H. A. and Steele, J. M. The behavior of renal blood flow after partial constriction of the renal artery. *J. Exper. Med.*, 72: 707, 1940.
42. Mason, M. F., Robinson, C. S. and Blalock, A. Studies on the renal arterial blood pressure and the metabolism of kidney tissue in experimental hypertension. *J. Exper. Med.*, 72: 289, 1940.
43. Kohlstaedt, K. G. and Page, I. H. The liberation of renin by perfusion of kidneys following reduction of pulse pressure. *J. Exper. Med.*, 72: 201, 1940.
44. Page, I. H. and Corcoran, A. C. Experimental Renal Hypertension, Springfield, Ill., 1948. Charles C Thomas.
45. Ogden, E. The organization of cardiovascular function. *Bull. New York Acad. Med.*, 24: 561, 1948.
46. Bahnson, H. T., Cooley, R. and Sloan, R. Cited by Bing.[14] To be published.

Blood Volume in Polycythemia as Determined by P^{32} Labeled Red Blood Cells*

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POLYCYTHEMIA vera is a disease characterized hematologically by an increase in the red blood count and hemoglobin and by an absolute increase in the total circulating red cell volume without obvious cause. As determined by the carbon monoxide,[1] Evans blue[2] and Congo red dye methods,[3–8] the blood volume in polycythemia vera has been found to be elevated due to an increase in the total red cell volume with little or no change in the plasma volume.

The total blood volume, as measured with carbon monoxide[10] and the trypan red,[11] Congo red,[12] Evans blue[9,26] and Geigy blue[23] dye methods, has been found to be increased in the polycythemia secondary to congenital heart disease due to an increase in the total red cell volume; the plasma volumes were low.

In this laboratory the determination of the blood volume has been of considerable diagnostic value in distinguishing between patients with absolute polycythemia, primary or secondary, and a relative polycythemia (high red blood count and hemoglobin due to a low plasma volume), and in determining precisely the actual degree of polycythemia before or after therapy.

METHODS

The blood volume was determined with P^{32} labeled red blood cells using a modification of the Hevesy and Zerahn[13] method for the labeling of red blood cells with P^{32} *in vitro*. Fifteen cubic centimeters of the patient's blood were withdrawn into a heparinized syringe. Five cubic centimeters of the patient's blood were placed in a 15-cc. graduated centrifuge tube which was covered with a rubber serum bottle stopper; 500 μc. of P^{32} as Na_2HPO_4 were added and incubated at 37°c. with constant rotation for approximately two hours. The cells were washed three times by adding isotonic saline solution, centrifuging and removing the supernatant fluid. The blood and saline were aseptically added to and removed from the centrifuge tube by the use of a long needle and an air vent consisting of a No. 20 needle, a short piece of rubber tubing and a short length of glass tubing containing a plug of cotton. Then the plasma obtained from the remainder of the patient's blood and containing no P^{32} was added to the cells to reconstitute whole blood. One cubic centimeter of this reconstituted whole blood was injected into an antecubital vein; after fifteen minutes 5.0 cc. of blood were withdrawn from another vein. A standard was prepared by diluting 1.0 cc. of the reconstituted blood in 2,000 cc. water.

The P^{32} was assayed by drying 0.1 cc. of blood on a piece of lens paper on a thin aluminum foil, wrapping the lens paper and aluminum foil in cellophane and counting on a 1B85 Thyrode counter tube.† In a similar manner 0.1 cc. of the standard and 0.1 cc. of the original blood taken from the patient were mounted and counted. The hematocrit was determined in Wintrobe hematocrit tubes.

RESULTS

The blood volumes were determined in sixty-six patients. These are recorded in Table 1 and graphically presented in Figure 1. The average total red cell volume

† Obtainable from Victoreen Instrument Company, Cleveland, O.

* From the Donner Laboratory of Medical Physics, the Radiation Laboratory and the Department of Physics, University of California, Berkeley, Calif. This study was supported by the U. S. Public Health Service.

TABLE I
BLOOD VOLUME IN POLYCYTHEMIA

Patient	Hematocrit	Total Red Cell Volume*	Plasma Volume*
Polycythemia Vera			
Group I:			
1 E. B.	58	45.6	33.0
2 C. G.	68	80.2	37.8
3 F. H.	70	51.0	21.7
4 H. K.	66	54.4	27.2
5 E. M.	57	42.4	32.0
6 R. R.	57	50.0	37.2
7 C. R.	61	66.7	42.7
8 H. S.	56	41.1	32.3
9 M. S.	55	31.3	25.6
10 H. S.	72	68.6	26.8
11 R. W.	72	57.6	22.4
12 E. B.	70.5	60.3	25.2
13 L. Y.	68	72.6	33.1
14 L. V.	63	48.0	27.4
15 L. A.	60	46.6	30.3
16 S. M.	56	47.7	34.9
17 E. J.	80	93.9	22.3
18 J. K.	60	38.8	25.9
19 L. H.	64	53.6	28.5
20 M. L.	59	34.9	24.2
21 J. W.	74	57.6	20.2
22 R. D.	55	38.1	31.2
23 M. D.	58	60.2	43.7
24 L. G.	67	51.6	25.3
25 E. K.	65	43.5	23.4
26 A. M.	73	50.2	18.6
27 W. M.	64	42.0	24.1
28 E. P.	61	55.8	35.7
29 N. F.	63	57.0	34.0
30 L. C.	70	49.3	19.7
31 S. J.	64.5	46.8	25.0
32 K. I.	58.5	53.1	36.3
Group II:			
1 H. C.	51	31.8	30.5
2 S. E.	51	39.4	38.0
3 A. F.	50	31.2	31.2
4 N. N.	54	46.4	39.6
5 L. P.	54	43.7	31.4
6 L. S.	52	40.8	37.7
7 E. V.	54	43.0	37.0
8 E. D.	52	39.0	36.0
9 F. P.	54	57.9	49.3
Group III:			
1 A. B.	41.5	24.7	34.8
2 T. F.	42	33.8	46.6
3 J. H.	49	27.1	28.3
4 A. I.	47	33.3	37.7
5 L. M.	38	21.7	35.4
6 L. M.	46.5	22.4	25.8
7 H. M.	38	21.8	35.6
8 C. S.	40	25.8	38.7
9 M. B.	46	24.5	28.9
10 E. B.	47	30.0	33.7
11 J. G.	42	24.1	33.3
12 A. P.	45	35.7	43.6

TABLE I (*Continued*)

Patient	Hematocrit	Total Red Cell Volume*	Plasma Volume*
Secondary Polycythemia			
1 D. F. (TF†)	70	75.9	32.6
2 H. S. (TF)	51	35.7	34.3
3 S. J. (TF)	75	68.2	20.4
4 F. M. (RC)	70	58.1	24.9
5 J. G. (PF)	59	46.5	32.3
6 A. N. (CP)	56	36.9	28.3
Relative Polycythemia			
1 J. A.	85	28.5	23.3
2 B. C.	51	27.0	25.6
3 D. F.	48	26.4	28.5
4 H. F.	59	34.0	23.6
5 A. L.	50	32.2	32.2
6 H. O.	49	34.0	29.2
7 D. S.	54	30.6	26.0

* Indicated in cubic centimeters per kilogram of body weight.

† TF, tetralogy of Fallot; RC, renal carcinoma; PF, pulmonary fibrosis; CP, cor pulmonale.

in normal individuals, as calculated from the values reported in the literature using Fe^{59} or washed P^{32} labeled red blood cells, is 29.9 cc./kg. with a range of 22.8 to 35.8 cc./kg. of body weight. In this laboratory in a series of twelve persons the average total red cell volume was 29.3 cc./kg. The average plasma volume was 38.7 cc./kg. and the range 32.6 to 45.1 cc./kg. of body weight.[14–16]*

Polycythemia Vera

There were fifty-three patients in this group in whom the blood volumes were determined before, during or after treatment with P^{32}.

Group I, Hematocrit 55 or Greater. There were thirty-two patients in this group. Thirty (No. 9 and No. 20 are the exceptions) showed elevated total red cell volumes ranging from 48.8 to 93.9 cc./kg. body weight. Twenty-two of these thirty-two patients had low plasma volumes. The

* As calculated from the total red cell volume and hematocrit (not from the data reported in these papers, using the dye methods).

plasma volume in eight of the remaining ten patients was under the average for normal but within the range of normal. Two patients had a plasma volume above the average but within the range of normal. Thus in polycythemia in relapse, with an

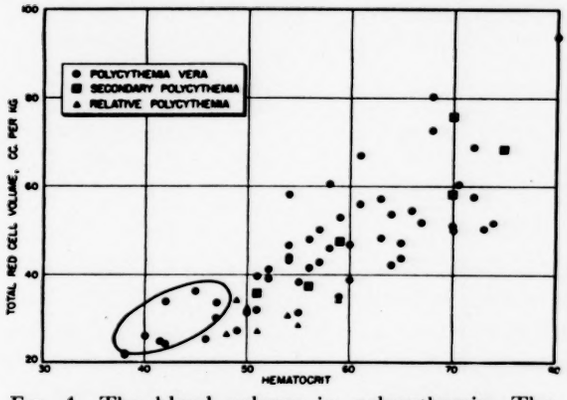

FIG. 1. The blood volume in polycythemia. The ellipse was calculated by the method of Smith[22] to include 92 per cent of the normal values reported in the literature.[14–16]

elevated hematocrit, there is usually an increased total red cell volume, a low plasma volume, and in 69 per cent of the cases, the plasma volume is lowered beyond the range of normal.

Group II, Hematocrit 50 to 54. Seven of the nine patients in this group had elevated total red cell volumes; in six of these seven patients the plasma volumes were close to the average for normal. Two patients showed normal total red cell volumes but had high hematocrits because of an unexplained low plasma volume.

Group III, Hematocrit under 50. Ten of the 12 patients in this group showed total red cell volumes within the normal range; two with hematocrits of 38 had low total red cell volumes. In three patients the hematocrit was falsely high due to a low plasma volume and in one falsely low because of a high plasma volume.

Secondary Polycythemia

Six patients had secondary polycythemia. There were three patients with tetralogy of Fallot, two untreated and one treated. The untreated patients revealed increased total red cell volumes and low plasma volumes. One patient treated with venesections had a high normal total red cell volume and plasma volume. One patient who had a renal tumor with x-ray evidence of pulmonary metastases showed a high total red cell volume and a low plasma volume. There

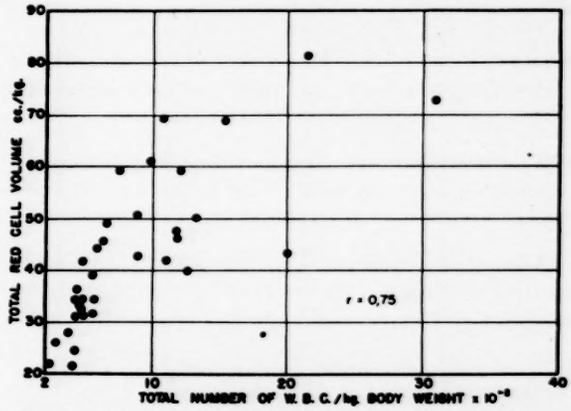

FIG. 2. The total number of white blood cells per kg. of body weight as a function of the total red cell volume in thirty-five unselected cases of polycythemia vera.

was one case of pulmonary fibrosis and one of cor pulmonale of unknown etiology.

Relative Polycythemia

There were seven patients in this group. These patients had either elevated red blood cell counts, or hematocrits due to a low plasma volume, of either known or unknown origin. The seven patients in this group all showed low plasma volumes, normal total red cell volumes, but either elevated red blood cell counts, hemoglobins or hematocrits as a result of the low plasma volume. The etiology of the low plasma volume could not be determined in six of these patients. One patient had multiple myeloma.[17] These seven patients were referred to this clinic with a diagnosis of polycythemia vera.

Figure 1 shows that the variation of the total red cell volume for a given hematocrit is so great that it is not possible to predict the total red cell volume from the hematocrit.

Figure 2 shows the relationship between the total number of circulating white blood cells, expressed in number of white blood cells per kilogram of body weight, and total

red cell volume, expressed in cubic centimeters per kilogram of body weight, in thirty-five unselected cases of polycythemia vera. There is a direct relationship between the increased total red cell volume and the total number of white blood cells, the correlation coefficient being 0.75. This is further evidence for the concept that in polycythemia vera there is hyperplasia not only of the red cell series but also of the myeloid series; it is also in agreement with the known fact that leukemia often occurs concomitantly with or as a complication of polycythemia vera.[24,25]

For diagnostic purposes the determination of the blood volume separates the polycythemia veras and secondary polycythemias from the relative polycythemias. The differentiation of polycythemia vera from secondary polycythemia is made by the history, physical examination and blood oxygen saturation, but it can not be done by blood volume determination as has been inferred.[3]

The highest and the average values reported with the carbon monoxide method, and in most of the reports using the dye methods, are much higher than have been found in this series of patients, e. g., the highest values are 189 cc./kg.,[1] 208 cc./kg.[2] and 209 cc./kg.[6] The values reported here are more in agreement with those observed by Haden although the higher values reported in his series for those patients with hematocrits greater than 70 are considerably higher than in this series.

The discrepancies in the general range for the blood volume in polycythemias between the carbon monoxide and dye methods and the labeled red blood cells is most probably due to the errors inherent in the dye and carbon monoxide methods. The carbon monoxide method may be criticized because some CO is bound to myoglobin.[18,19] Evans blue (T-1824) is thought to give high values for the plasma volume because of the disappearance of the dye from the blood stream[27] and also because of the subsequent appearance of some of the dye in the lymph.[20] Although the carbon monoxide, the dye and labeled red blood cells methods have been compared with one another in normals,[16,21] there is only one report of a comparison of the dye methods and labeled red blood cells in diseased states which show considerable variation in some of the individual cases.[15]

CONCLUSIONS

The blood volume has been determined in fifty-three cases of polycythemia vera, six cases of secondary polycythemia and seven cases of relative polycythemia.

Polycythemia vera. (1) In polycythemia vera thirty of the thirty-two patients with a hematocrit of 55 or greater had elevated total red cell volumes; twenty-two had low plasma volumes; eight were under the average and two above average. However, all were within the range for normal. One showed increased plasma volume. (2) Of nine patients with hematocrits of 50 to 54 inclusive, seven had elevated total red cell volumes; the other two subjects had low plasma volumes so that they had falsely high hematocrits. (3) The twelve patients with hematocrits under 50 had normal or low total red cell volumes. There were three patients with low and one with a high plasma volume.

Secondary Polycythemia. The five untreated patients in this group had elevated total red cell volumes and low plasma volumes.

Relative Polycythemia. The patients in this group had normal total red cell volumes but had high hematocrits due to an unexplained low plasma volume.

The absolute polycythemias can be differentiated from the relative polycythemias by blood volume determinations. Secondary polycythemias cannot be differentiated from polycythemia vera by the determination of the blood volume.

The variation of total red cell volume with hematocrit for a given hematocrit is too great to permit the prediction of the total red cell volume from the hematocrit.

There is a direct correlation (0.75) between the total red cell volume and the number of circulating white blood cells.

REFERENCES

1. Boycott, A. E. and Douglas, C. G. The total oxygen capacity and blood volume in three cases of splenomegalic polycythemia. *J. Path. & Bact.*, 13: 117, 1908.
2. Gibson, J. G., II, Harris, A. W. and Swigert, V. W. Clinical studies of the blood volume VII: macrocytic and hypochromic anemias due to chronic blood loss, hemolysis and miscellaneous causes, and polycythemia vera. *J. Clin. Investigation*, 19: 621, 1939.
3. Haden, R. L. The red cell mass in polycythemia in relation to diagnosis and treatment. *Am. J. M. Sc.*, 196: 493, 1938.
4. Rowntree, L. G., Brown, G. E. and Roth, G. M. The Volume of the Blood and Plasma in Health and Disease. Philadelphia, 1929. W. B. Saunders Co.
5. Hartwich, A. and May, G. Blutmengenbestimmungen mittels Farbstoffmethode. *Ztschr. f. d. ges. exper. Med.*, 51: 497, 1926.
6. Brown, G. E. and Giffin, H. Z. Studies of the vascular changes in cases of polycythemia vera. *Am. J. M. Sc.*, 131: 171, 1926.
7. Bock, A. V. Constancy of volume of blood plasma. *Arch. Int. Med.*, 27: 83, 1921.
8. Lampe, W. Blutmengenbestimmungen bei Polycythemia vera (Vaquez). *Deutsche. med. Wchnschr.*, 51: 2025, 1925.
9. Hallock, P. Polycythemia of morbus caeruleus (cyanotic type of congenital heart disease). *Proc. Soc. Exper. Biol. & Med.*, 44: 11, 1940.
10. Parkes-Weber, F. and Dorner, G. A case of congenital pulmonary stenosis, with special consideration of the nature of the secondary blood changes. *Lancet*, 1: 150, 1911.
11. Blumenfeldt, E. and Wolheim, E. Zur klinischen Beurteilung angeborener Herzfehler. *Klin. Wchnschr.*, 6: 396, 1926.
12. Meyer, P. Hämodynamik und Hämophysikochemie bei einem Fall von Ventrikelseptumdefekt mit Pulmonalstenose. *Ztschr. f. klin. Med.*, 120: 341, 1932.
13. Hevesy, G. and Zerahn, K. Determination of red corpuscle content. *Acta physiol. Scandinav.*, 4: 376, 1942.
14. Gibson, J. G., II, Peacock, W. C., Seligman, A. M. and Sack, T. Circulating red cell volume measured simultaneously by the radioactive iron and dye methods. *J. Clin. Investigation*, 25: 838, 1946.
15. Mayerson, H. S., Lyons, C., Parson, W., Nieset, R. T. and Tratuman, W. V., Jr. Comparison of results of measurement of red blood cell volume by direct and indirect technics. *Am. J. Physiol.*, 155: 237, 1948.
16. Reeve, E. B. and Veall, N. A simplified method for the determination of circulating red-cell volume with radioactive phosphorus. *J. Physiol.*, 108: 12, 1949.
17. Lawrence, J. H. and Rosenthal, R. L. Multiple myeloma associated with polycythemia. *Am. J. M. Sc.*, 218: 149, 1949.
18. Asmussen, E. On determination of blood volume by CO method. *Acta physiol. Scandinav.*, 3: 156, 1944.
19. Pace, N. Personal communication.
20. Cardozo, E. L. The disappearance of the blue dye T-1824 from the blood stream into the thoracic duct lymph. *Arch. néerl. de physiol.*, 25: 410, 1941.
21. Hopper, J., Jr., Tabor, H. and Winkler, A. W. Simultaneous measurements of the blood volume in man and dog by means of Evans blue dye, T-1824, and by means of carbon monoxide: I. Normal subjects. *J. Clin. Investigation*, 23: 628, 1944.
22. Smith, H. W. Note on the interpretations of clearance methods in the diseased kidney. *J. Clin. Investigation*, 20: 637, 1941. Correction in Smith, H. W. Lectures on Kidney. Lawrence, Kansas, 1943. Univ. Kansas Press.
23. Prader, von A., Rossi, E. and Wodenegg, Melitta. Blutuntersuchungen beim Morbus Coeruleus. I. Plasma- und Blutvolumen. *Helvet. Paediat. acta*, 4: 267, 1949.
24. Wasserman, L. R., Lawrence, J. H., Dobson, R. L. and Estren, S. The bone marrow picture in polycythemia vera before and after treatment with radioactive phosphorus. (To be published.)
25. Lawrence, J. H. The control of polycythemia by marrow inhibition; a ten year study on 172 patients. *J. A. M. A.*, 141: 13, 1949.
26. Nelson, Woodrow, Mayerson, H. S., Clark, John H. and Lyons, Champ. Studies of blood volume in the tetralogy of Fallot and in other types of congenital heart disease. *J. Clin. Investigation*, 26: 853, 1947.
27. Lawson, H. C., Overbey, D. T., Moore, J. C. and Shadle, O. W. Mixing of cells, plasma and dye T-1824 in the cardiovascular system of barbitalized dogs. *Am. J. Physiol.*, 151: 282, 1947.

Hypercoagulability of the Blood Associated with ACTH and Cortisone Therapy*

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DURING the course of treatment of patients with ACTH or cortisone at this institution a number of thromboembolic complications have been observed. While these patients were ill with diseases which *per se* might have led to intravascular thrombosis, the possibility existed that ACTH or cortisone might have promoted a thrombotic tendency by producing a state of hypercoagulability of the blood. In order to clarify this point a study of the blood coagulation mechanism was undertaken in patients receiving treatment with these agents.

METHODS

Patients who were to receive ACTH or cortisone therapy were selected from the wards of the Presbyterian Hospital. The diagnoses of these subjects included a variety of disease states, such as disseminated lupus erythematosus, rheumatoid arthritis, uveitis, sarcoidosis, pulmonary fibrosis, thrombocytopenic purpura and the nephrotic phase of chronic glomerulonephritis. In the majority of instances coagulation tests were obtained prior to and at one or more selected points during therapy. In several instances tests were not obtained prior to institution of therapy but during and following administration of ACTH or cortisone.

Venous clotting times were determined according to a modification of the Lee-White technic.[1] Four chemically clean, 75 by 10 mm. test tubes, a syringe and a 20-gauge needle were rinsed with physiologic saline solution. Following a cleanly negotiated venipuncture, 1 cc. of blood was placed in each tube. Clotting was considered to have occurred when, following complete inversion of the tube, tapping of the tube with a finger did not produce movement of liquid blood. Normal values with this technic range up to twenty minutes.

In order to magnify the changes observed in the standard venous clotting time, heparin-retarded venous blood coagulation time determinations were carried out according to the Waugh-Ruddick modification[2] of the Lee-White technic.[1] Four chemically clean 75 by 10 mm. test tubes, a syringe and a needle were rinsed with isotonic saline solution. Into each test tube 0.5 cc. of a saline solution containing 0.5 units of heparin was measured with a 1 cc. tuberculin syringe. Following a cleanly negotiated venipuncture, 1 cc. of blood was placed in each tube and the tube inverted twice to mix the heparin solution with the blood. The same end point was adopted as for the venous clotting time. The normal range is between forty-five and seventy minutes.

Prothrombin time determinations were performed on whole plasma according to the Link-Shapiro modification[3] of Quick's technic,[4] using 0.1M sodium oxalate as the anticoagulant, commercially supplied rabbit lung as the source of thromboplastin and 0.025M calcium chloride. Normal values in this laboratory are 13 ($\pm$ 2) seconds.

Fibrinogen B determinations were performed according to the technic of Cummine and Lyons.[5] Four and one-half cc. of blood were obtained by a cleanly negotiated venipuncture and was placed in a test tube which contained 0.5 cc. of 0.1M sodium oxalate. The plasma was separated by centrifugation and 1 cc. of plasma was pipetted into a test tube. To this were added 5 drops of a prepared reagent solution of β-naphthol and the mixture was allowed to stand for ten minutes before it was examined for clot formation. Normally no fibrinogen B is present. The positive values ranged from + to +++.

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Protamine titrations were performed according to the technic of Allen.[6] Following a cleanly negotiated venipuncture, 11 cc. of blood were placed in a test tube to which 1 mg. of sodium heparin had been previously added and the tube was inverted three times. Within two hours one cc. of blood was pipetted into each of ten 75 by 10 mm. glass test tubes. Protamine sulfate was then added to the test tubes beginning with 80γ and increasing at increments of 20γ. Each tube was inverted three times and the tubes were allowed to stand for one hour at room temperature. The end point was the formation of a solid gelled clot and the result was expressed as the smallest amount of protamine producing the gel. The range of normal in this laboratory is 120 to 160γ.

TABLE I

EFFECT OF ACTH AND CORTISONE ON BLOOD COAGULATION

Patient	Age, Sex	Diagnosis	Drug	Daily Dosage (mg.)	Tests	Control	Day of Therapy								
							2	3	4	5	6	7	8	10	11	12
1. V. N.	19 F	Disseminated lupus erythematosus	ACTH	100	* V.C.T.	14 ..	9	5	..	..	..	..	..	..	..	..
					† Hep. V.C.T.	84 ..	46	14	..	..	..	..	..	..	..	..
2. F. M.	22 F	Acute pulmonary fibrosis	ACTH	100–5 days	V.C.T.	20 20	12	6	..	..	8	..	12	..	..	13
				50–10 days	Hep. V.C.T.	57 59	35	35	..	..	28	..	39	..	..	48
							25									
3. E. P.	28 F	Pulmonary fibrosis	ACTH	100–1 day	V.C.T.	22 19	10	..	8	..	..	..	..	..	..	..
				50–8 days	Hep. V.C.T.	62 54	46	..	43	..	..	..	..	..	..	..
4. E. H.	26 F	Sarcoidosis	ACTH	100-1 day	V.C.T.	17 18	12	..	10	..	..	..	..	..	..	..
				50-8 days	Hep. V.C.T.	63 66	39	..	35	..	..	..	..	..	..	..
5. S. S.	54 M	Uveitis	Cortisone	100	V.C.T.	15 15	..	..	..	10	..	..	..	..	11	..
										11						
					Hep. V.C.T.	56 60	..	..	..	35	..	..	..	..	44	..
										33						
6. M. T.	62 F	Uveitis	Cortisone	100	V.C.T.	13 13	..	..	..	10	..	..	..	..	14	..
										12	..	..	..	..	17	..
					Hep. V.C.T.	40 43	..	..	..	30	..	..	..	..	32	..
										29	..	..	..	..	42	..
7. M. C.	60 F	Thrombocytopenic purpura	ACTH	80	V.C.T.	12 ..	..	..	..	13	12	9	..	3	..	..
8. M. K.	62 F	Neurodermatitis	Cortisone	100	V.C.T.	17 17	..	..	..	12	..	..	..	..	..	..
9. Z. A.	49 F	Uveitis, rheumatoid arthritis	Cortisone	100	V.C.T.	20 ..	..	..	..	..	9	..	..	..	..	..
10. A. V.	48 M	Uveitis	Cortisone	100	V.C.T.	19 ..	..	..	..	..	..	..	13	..	..	..

* V.C.T. = Venous clotting time.
† Hep. V.C.T. = Heparin-retarded venous clotting time.

RESULTS

Venous Clotting Time. Eight of ten patients showed considerable shortening of the venous coagulation time while receiving ACTH or cortisone. (Table I.) Five of these eight were given ACTH and three received cortisone. The two remain ng subjects, both with chronic active uveitis and iritis, received 100 mg. of cortisone daily without significantly affecting their coagulation time.

One woman with long-standing documented Addison's disease showed a clotting time of ten minutes on the twenty-third day of cortisone (100 mg. daily) treatment. This patient not only exhibited the typical clinical picture of hypo-adrenalism, including pigmentation and low serum sodium values on salt restriction, but also excreted 0.91 mg. of neutral reducing lipids in twenty-four hours and had no eosinophile decrease following the administration of 50 mg. of ACTH. Six days after stopping cortisone administration the clotting time was eleven minutes; seventeen days later it was fifteen minutes. (Table II.)

Heparin-retarded Venous Clotting Time. Four of six individuals demonstrated a considerable decrease in the heparin-retarded venous coagulation time while receiving ACTH. Two others to whom cortisone was given failed to exhibit significant maintained reduction of the clotting time.

The patient with Addison's disease had a heparin-retarded clotting time of thirty-two

minutes on the twenty-third day of cortisone (100 mg. daily) therapy. Six days after stopping cortisone the heparin-retarded clotting time was forty-two minutes; twenty-three days after stopping cortisone it had risen to sixty-three minutes. (Table II.)

The eleven thromboembolic episodes occurred among approximately 175 patients who received ACTH or cortisone for varying lengths of time.

The results of the present studies on the coagulation time and heparin-retarded coagulation time indicate that ACTH and cortisone produce a state of hypercoagulability of the blood. In three patients hypercoagulability was maintained for as long as seven to fifteen days after discontinuance of ACTH or cortisone.

TABLE II

STUDIES OF THE COAGULATION MECHANISM IN A PATIENT WITH ADDISON'S DISEASE TREATED WITH CORTISONE

Patient	Age, Sex	Diagnosis	Drug	Daily Dose (mg.)	Tests	Receiving Cortisone Day 23	After Stopping Cortisone	
							Day 6	Day 23
G. S.	55 F	Addison's disease	Cortisone	100	V.C.T.* Hep. Ret. V.C.T.†	10 32	11 42	15 63

* V.C.T. = Venous clotting time.
† Hep. Ret. V.C.T. = Heparin-retarded venous clotting time.

Prothrombin Time. No consistent change to a state of hyper- or hypoprothrombinemia was observed in eleven patients.

Fibrinogen B. There was no maintained significant increase in fibrinogen B in six subjects. In four others in whom determinations were made, but only during the period of ACTH or cortisone treatment, fibrinogen B was positive (+) in only one patient.

Protamine Titration. In six patients there was no significant change in the protamine titration. In five additional subjects protamine titration determinations were obtained only while receiving these agents and all were within the normal range.

COMMENTS

Two deaths due to pulmonary embolism have been observed at the Presbyterian Hospital during therapy with ACTH or cortisone. In addition, during or within two weeks after therapy three instances of nonfatal pulmonary embolism have occurred (one of which was associated with bilateral deep phlebitis of the legs), one superficial thrombophlebitis of the saphenous vein, two definite and one probable phlebothrombosis of the deep veins of the leg, one radial artery thrombosis and one cardiac infarction.

Figure 1 illustrates the markedly altered coagulability observed in a nineteen year old woman (No. 1 in Table I) with disseminated lupus erythematosus who was given 100 mg. of ACTH daily in four divided doses. On day 3, when the maximum effect on coagulation was present as indicated by the venous clotting and heparin-retarded venous clotting time, venous blood was drawn for a prothrombin time determination but clotted in the test tube despite the presence of a usually adequate amount (0.5 cc.) of 0.1 M sodium oxalate. This suggested the possibility that the altered state of coagulation may be due in part to a preformed thrombin molecule, such as the thrombin A described by Lyons,[7] inasmuch as the oxalate solution in the test tube did not prevent the *in vitro* coagulation of the fibrinogen. Because fatal embolism had occurred one week prior to these observations in a young woman with disseminated lupus who had been treated

with ACTH (100 mg. daily) for two and one-half days, this patient was immediately placed on prophylactic heparin and dicumarol therapy for five days. No thromboembolic episode occurred and ACTH was stopped after a total duration of seven days.

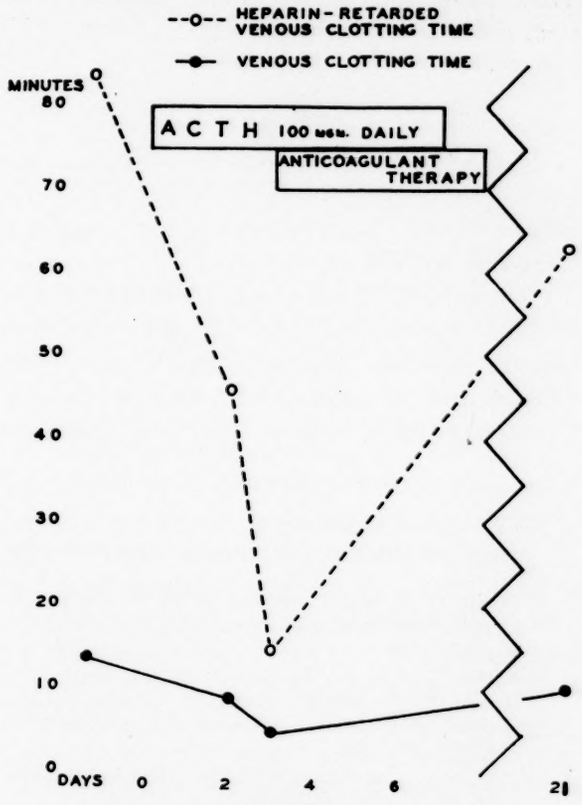

FIG. 1.

In determinations made two weeks after cessation of anticoagulant therapy the venous coagulation time and the heparin-retarded venous coagulation time had returned toward their values prior to ACTH.

The dosage of ACTH or cortisone may be an important factor in determining the degree of hypercoagulability produced. This possibility is supported by the results (Fig. 2) obtained in a twenty-one year old woman (No. 2) with severe pulmonary fibrosis, who for the first five days was given 25 mg. of ACTH every six hours, after which the dosage was reduced to 12.5 mg. every six hours. In this patient a moderate degree of hypercoagulability was noted while receiving the larger dosage of ACTH, followed by a definite decrease in the degree of coagulability after the ACTH dosage was reduced. It appears that ACTH in dosage of 100 mg. daily is more effective than cortisone in dosage of 100 mg. daily in causing a hypercoagulable state.

The mechanism of this change in blood

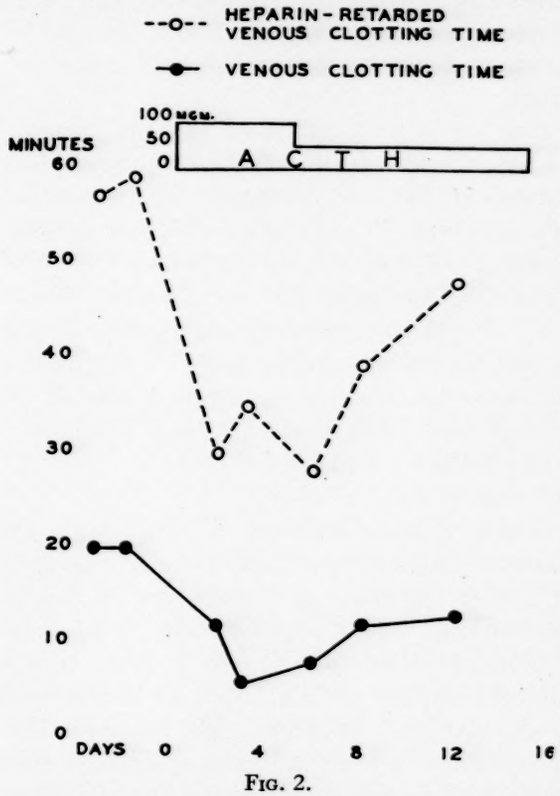

FIG. 2.

coagulation is not clear. From these studies it appears that fibrinogen B is not the cause of the increased coagulability. Furthermore, the failure to observe changes in protamine titration while receiving ACTH or cortisone may be interpreted as indicating no decrease or increase in the naturally occurring heparin-like substances. This was supported by investigating the *in vivo* tolerance to heparin (10 mg. given intravenously) in several persons receiving ACTH or cortisone. No significant change was observed from the usual response to this dosage of heparin.

No indication that a state of hyperprothrombinemia is produced by ACTH or cortisone was given by the results of one-stage prothrombin time determinations. This finding was complemented by observa-

tions of the response of ACTH- or cortisone-treated individuals to the administration of dicumarol. In none of this group was an increased resistance to dicumarol observed. In fact, these latter studies suggest that patients receiving ACTH or cortisone may be unusually sensitive to dicumarol and thus may require significantly lower dosage of dicumarol to produce an anticoagulant effect.

Further investigation of the mechanism of the altered state of blood coagulation during ACTH and cortisone administration is under way. Qualitative or quantitative changes in the blood thromboplastin or thromboplastinogen may be effected. However, the prothrombin consumption, which is considered a reflection of the plasma thromboplastic activity, was not altered in a hemophilic boy studied in this laboratory while being treated for four days with ACTH (25 mg. every six hours).

These studies indicate the necessity for maintaining an awareness of the potentiality of these agents for producing a "prethrombotic state," particularly in patients in whom other factors are present which also predispose to intravascular thrombosis (e.g., bed rest, infection, postoperative and postpartum state, malignancy, cardiac failure, etc.). In such individuals the combination of the underlying disease state plus the hypercoagulability secondary to ACTH or cortisone administration may act synergistically to precipitate intravascular coagulation. In light of the observations recorded it may prove advisable to employ prophylactic anticoagulant therapy under such circumstances, particularly in clinical situations demanding continuance of ACTH or cortisone.

It is possible that excessive coagulability of the blood associated with the hyperadrenal state may have some bearing on mechanisms of clinical thromboembolic disease.

SUMMARY

Numerous thromboembolic episodes, including two cases of fatal pulmonary embolism, have been observed in patients receiving ACTH or cortisone.

Changes have been observed in the venous clotting time and the heparin-retarded venous clotting time which indicate that ACTH and cortisone frequently produce a hypercoagulable state of blood coagulation.

REFERENCES

1. Lee, R. I. and White, P. D. A clinical study of the coagulation time of blood. *Am. J. M. Sc.*, 145: 495, 1913.
2. Waugh, T. R. and Ruddick, D. W. A test for increased coagulability of the blood. *Canad. M. A. J.*, 50: 547, 1944.
3. Shapiro, S., Sherwin, B., Redish, M. and Campbell, H. A. Prothrombin estimation; procedure and clinical interpretations. *Proc. Soc. Exper. Biol. & Med.*, 50: 85, 1942.
4. Quick, A. J. The nature of the bleeding in jaundice. *J. A. M. A.*, 110: 1658, 1938.
5. Cummine, H. and Lyons, R. N. A study in intravascular thrombosis with some new conceptions of the mechanism of coagulation. *Brit. J. Surg.*, 35: 22, 1948.
6. Allen, J. G., Maulder, P. V., Sanderson, M. H., Egner, W. M. and Crosbie, J. *J. Lab. & Clin. Med.*, 34: 473, 1949.
7. Lyons, R. N. Personal communication.

Review

Sickle Cell Anemia*

Clinical Study of Fifty-four Cases

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THE benign and pernicious forms of sickling result from an unknown inherited abnormality of the erythrocyte. It is generally believed that mechanical hemolysis, resulting anemia and vascular occlusion give rise to the protean disturbances of sickle cell disease. The clinical manifestations of the disease have been adequately described[1,2] and are well known. However, because of the debilitating prolonged manifestations, lack of therapeutic success and ignorance of the basic cause of the erythrocyte defect further investigation of all phases of sickle cell disease is indicated. In this communication clinical findings in a significantly large series of cases are presented. When feasible, available material is utilized to correlate organic dysfunction with the anemic state. The data were obtained from the clinical records of patients admitted to the charity hospitals of this area.

Clinical records of fifty-four patients, having 105 admissions to the medical services between 1939 and 1949, were analyzed. This does not include all patients with sickle cell anemia in this area nor does it include all admissions for the fifty-four patients. The population sample of which this series deals consists of twenty-six females and twenty-eight males whose families were usually in the low income bracket. Relationship between geographic distribution of birth and incidence of the disease could not be established; the patients in this series compare favorably with the over-all Negro population in this area. Cases of doubtful sickle cell anemia were usually excluded. Since 1945 cases of this type have been excluded by the routine utilization of the diagnostic parameter[3] and studies of *in vivo* sickling.[4] Subsequent reports will describe these latter findings in more detail.

Eight subjects below the age of twelve are included in this study. The youngest patient in the series was five years of age, the oldest was fifty. The mean age was 21.2 years; the mode age was twenty to twenty-four years. There were three patients over forty years of age. Since pain often indicated to the patient that he or she was ill, case histories routinely obtained overlooked such symptoms as childhood easy fatigability and frequent yellow discoloration of the eyes. In a series of twenty-six cases personally observed the onset of debilitating pain varied from the age of three to the age of twenty-two. Careful questioning of all elicited the information that during early childhood there was inability to play as long as other children in the same age group because of easy fatigability.

In Table 1 the presenting signs and symptoms are outlined and were frequently combined. Anemia, pain, fever and jaundice, associated with cardiac murmurs, in a Negro patient suggest the diagnosis which is confirmed by sickling on the thin smear, in the counting chamber or by studies of *in vivo* sickling. Although habitus was not usually described, observations by Sharp and Vonder Heide,[5] as well as personal

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observations by the author, confirmed the generally eunuchoid habitus of these patients.

Pain. This was a variable symptom. The extremities, with or without confinement to the joints, were the most frequent sites of pain. Other sites were the abdomen and chest. Pain occasionally was described as "everywhere." During hospitalization changes in the site as well as frequent recurrences while inactive were noted. Duration was variable and lasted from a few minutes to several days or weeks. It was usually sudden in onset and often disappeared as suddenly. Attacks frequently awakened the subject from sleep. Two females had a history of attacks of pain in the joints at time of menstruation.

TABLE I

PRESENTING SIGNS AND SYMPTOMS OF FIFTY-FOUR CASES OF SICKLE CELL ANEMIA*

Anemia	54
Pain	49
Fever	40
Jaundice	34
Cardiac murmurs	32
Palpable liver	18
Pulmonary infection	14
Lymphadenopathy	14
Ulcer of lower extremities	9
Palpable spleen	3
Abscess (osteomyelitis)	3
Priapism	3
Hematuria	3
Subcutaneous nodules	2
Epistaxis	2
Cholelithiasis	1
Retinal hemorrhage	1
Subarachnoid hemorrhage	1
Weakness and pallor†	1

* Since symptoms were often reduplicated on subsequent admissions, this table refers only to signs and symptoms as might be presented at any one time in the total fifty-four cases.

† All patients had weakness. The one case had never had any other symptoms and was admitted only for a blood transfusion because he "appeared weak."

Fever. All attacks of severe pain were accompanied with fever that was usually irregular. It was noted on several occasions when the patient was otherwise asymptomatic. The maximum fever was over 106°F. The mean maximum fever was 102°F. Duration of fever varied from one to thirty days with a mode of five days.

Jaundice. Thirty-four patients were described as revealing evident jaundice. Fifty-one routine serum bilirubin determinations were obtained. Twenty revealed an elevated direct-reacting bilirubin; twenty revealed an elevated indirect- or delayed-reacting bilirubin. The remainder were within normal limits with only the total serum bilirubin reported. During quiescent phases of the disease the indirect test predominated.

Liver. Enlarged livers were smooth, presented variable degrees of tenderness and frequently returned to normal size within a few days. High elevated direct bilirubin tests were associated with the largest and most painful livers, although palpable, tender livers were frequently found associated with the elevated, indirect bilirubin test. Cholelithiasis was found in one patient but no direct-reacting bilirubin resulted from large duct obstruction. In five cases severe jaundice was sudden in onset, gave a direct reaction and the patients presented a picture of severe fulminating hepatitis.

Reports of liver function studies in this disease must be critically evaluated. The severe anemia, protean disturbances, questionable kidney damage and nutritional status of the patient must be considered. Inadequacy of study of an important element of hepatic function, the reticulo-endothelial system, would likewise diminish the importance of any thorough function study.[6] In view of severe hemolysis, urine urobilinogen studies are of no value. The indirect-reacting bilirubin is of more importance as an index of hemolysis than of hepatocellular damage. The direct-reacting bilirubin, when cholelithiasis is excluded, is of prime importance and suggests associated cholangiolar dysfunction. Fecal urobilinogen studies were sometimes obtained and will be presented in a subsequent paper. It was noted, however, that with marked cholangiolar damage there was decrease in fecal urobilinogen; and when no definite evidence of liver damage existed, fecal urobilinogen was high.

In this series of cases the usual battery of

liver function tests was not routinely obtained; however, in Table II the available data which might be significant are presented. Liver function study based on the reacting bilirubin is arbitrary and is presented because of the importance of the direct bilirubin when determining hepatic damage after cholelithiasis is excluded.

TABLE II
LIVER FUNCTION STUDIES

	Normal Total Serum Bilirubin or Elevated Indirect-Reacting Serum Bilirubin			Elevated Direct-Reacting Serum Bilirubin		
	Number	Positive	Negative	Number	Positive	Negative
Cholesterol	13	2	11	6	6	0
Alkaline phosphatase	..	..	..	9	1	8
Cephalin-cholesterol flocculation test	1	..	1	6	6	..
Bromsulfalein	7	0	7	3	1	2

The serum cholesterol values are utilized with the knowledge that in chronic hemolytic states the total is usually decreased. Analysis indicates that when evidence of liver dysfunction is based on the predominant reacting bilirubin, 150 mg. per cent becomes a significant value. With the direct test the maximum was 214 mg. per cent with all values being above 150 mg. per cent. With the indirect or normal tests the minimum was 60 mg. per cent and only two were over 150 mg. per cent. These patients presented a serum cholesterol of 168 mg. per cent and 195 mg. per cent, and an indirect bilirubin of 1.2 mg. per cent and 0.9 mg. per cent. The highest serum cholesterol of 214 mg. per cent was obtained in a patient who expired with evidence of severe hepatic dysfunction. The serum bilirubin content varied from 4.8 mg. per cent on entrance to 19 mg. per cent just before death. Serum cholesterol values diminished to 100 mg. per cent just before death. This suggested increasing hepatocellular damage.

The alkaline phosphatase values remained below 10 Bodansky units in all except one case. This subject presented a progressively diminishing direct-reacting bilirubin. There was a severe osteomyelitis and the patient finally expired. The alkaline phosphatase value was only 13.5 Bodansky units. The bromsulfalein excretion studies were obtained on patients not presenting evident jaundice. One patient, age forty-one, with a previous history of numerous crises, revealed no significant retention of the dye. Three patients with less than 5 per cent retention of the dye had previous episodes of severe hepatic involvement within the past three months. The positive excretion study had a serum direct bilirubin of only 1.4 mg. per cent. Cephalin-cholesterol flocculation studies indicated hepatocellular damage and were usually obtained when visible jaundice was present.

Seventeen serum protein concentration studies revealed a slight increase in globulin in nine determinations. The maximum globulin concentration was 4.9 gm. The mean increased globulin concentration was 3.9 gm. Serum albumin concentration was decreased in five cases. No definite relationship could be established between hepatic involvement and serum protein disturbances.

Spleen. The spleen was described as palpable in three adults. Four patients had had splenectomy. No effect had been noted on the course of the disease. One patient continued to have left upper quadrant pain although the spleen was previously removed.

Kidney. Routine urinalyses were obtained on each admission. Seventeen patients revealed an appreciable albuminuria at some time. Only four patients, however, had a significant concentration above 2 plus. These four patients had blood urea nitrogen retention varying from 90 mg. per cent to 150 mg. per cent. Two have expired and are included in the group having severe hepatic damage. A third patient, under observation, is believed to have an associated nephrosclerosis and is the only one in this series who could be considered as hypertensive.

Specific gravity determinations varied in repeat studies from 1.002 to 1.015. Only two patients had concentrations above 1.015 at any time. Dehydration and hyperthermia had no effect upon the urine concentration.

Isolated renal function studies were obtained. Standard urea clearances were within normal limits in two patients. Two phenolsulfonphthalein studies revealed normal excretion of the dye in one patient and retention of the dye in another. The latter patient was recovering from a severe crisis with hepatic involvement. Hematuria occurred in three patients. Retrograde pyelograms obtained in two of these patients indicated no demonstrable damage.

Heart. Roentgenoscopic examination of the heart in thirty-nine subjects confirmed the presence of cardiac enlargement in twenty-seven. The typical mitral configuration of rheumatic heart disease was observed in only nine patients. The others had either generalized enlargement or left ventricular enlargement. Significant variations in size, with a return to normal at some time, were observed in serial roentgenograms of three patients.

Thirty-seven electrocardiograms were obtained in thirty subjects. The precordial leads of Wilson and the unipolar leads of Goldberger were utilized in all cases except one. Three patients were examined serially. Myocardial ischemia was indicated by changes in the T waves and displacement of the S-T segment. Twelve patients revealed definite evidence of myocardial ischemia. Serial electrocardiograms in two patients revealed variations in ischemia with a return to normal some time during the period of hospitalization. The third patient revealed progressive P wave changes with notching and an associated decrease in the degree of T wave inversion. Correlation of *in vivo* sickling and myocardial ischemia was not routinely attempted but four patients with over 50 per cent sickling of the erythrocytes revealed no evidence of myocardial ischemia by the accepted methods. Patients showing a return of T waves to the upright position had repeated blood transfusions. Auricular fibrillation was noted in one case. Other changes in this patient, including severe congestive failure, and a mitral configuration suggested rheumatic heart disease as a complicating factor. This subject had a previous history of prolonged anemia. At the last examination the erythrocyte count was 3.8 million with only approximately 10 per cent abnormal forms and no typical crescent forms.

Sound tracings were not obtained in any of these patients. The murmurs were described as mitral systolic in twenty cases. A pulmonic systolic murmur was described in five cases. A mitral diastolic murmur was described in five cases and an aortic systolic murmur in two cases. One patient apparently presented a transitory aortic diastolic murmur.

Lungs. Fourteen patients presented pneumonia. Productive cough with frothy, mucopurulent or blood-streaked sputum, pleural pain and fever, were the usual manifestations. Thirteen patients had associated typical crises with abdominal pain, severe joint pain and jaundice. Fever was prolonged and was noted to vary from four days to a maximum of thirty days. Routine examination of sputa was not confirmatory for specific etiologic agents. No evidence of increased titer could be found on examinations for cold agglutinins in three subjects. The response to antibiotic therapy was not conclusive. All cases were confirmed by x-ray and none had the appearance of infarct. Slow clearing of the pneumonia was usually noted.

Other Manifestations. The nervous system, bone, skin and lymph nodes were occasional sites of evident pathologic change. One patient with subarachnoid hemorrhage was believed to have an aneurysm at the base of the brain. Angiograms were not confirmatory and two years have elapsed with no further attacks. Meningeal irritations were occasionally seen during severe crises. Mental deficiency was definite in three cases. Hysteria was marked in two cases.

Bone changes are well known and have recently been adequately described.[7,8] In this series thirty-three subjects had x-rays for bone changes. Only fifteen revealed changes in bone consistent with a prolonged hemolytic anemia.

Healed ulcers were not usually noted on the clinical records. Three subjects stated that ulcers were their only knowledge of a chronic illness. The oldest patient in the series had large ulcers of the lower extremities and stated that they had been present since childhood. Two patients had severe varicose veins to complicate the etiology of the ulcers. At the present time one patient has had continued hospitalization for the past five months for therapy of the ulcers. Subcutaneous nodules, resembling erythema nodosum, were associated on two occasions with osteomyelitis. These nodules were usually transitory and disappeared in a few days.

Lymphadenopathy was common. Three biopsy reports confirmed simple hyperplasia as the cause. No mention was made of the presence of sickled cells in the specimen. One patient presented marked enlargement of the mediastinal nodes and was believed to have an associated lymphoma. At the present time, two years after onset, there has been no change in the size of the nodes.

Hematologic Studies. Sherman's[4] method for the determination of *in vivo* sickling was utilized in twenty-six cases. Marked variation in the degree and character of the sickling was noted. The diagnostic parameter on these same patients was in the range acceptable for diagnosis of sickle cell disease. These findings will be reported in a subsequent paper.

Admission erythrocyte counts or hemoglobin content were obtained in all cases of sickle cell anemia. The lowest admission erythrocyte count recorded was 1.1 million. The highest was 4 million; the mode was 2 to 3 million. With the exception of one case all could be classified as moderately severe or severe anemias. Normoblastosis and reticulocytosis were usual findings. Leukocytosis occurred on seventy-five admissions. The highest count recorded was 60,000. There was one leukopenia. Eosinophilia was noted in 45 per cent of the cases some time during their period of hospitalization.

Admission and discharge erythrocyte counts are presented in Table III. This table also includes the leukocyte count, reticulocyte count, amount of blood administered and the severity of the attack graded from I to IV. There was no significant change in the admission and discharge erythrocyte counts except in those patients given blood transfusions just before discharge. Since all patients not expiring were usually asymptomatic on discharge, disappearance of symptoms is not a result of elevation of the evident erythrocyte count. Note that there may be little difference in the discharge count and the admission count on the next admission.

Depression of the reticulocytes was noted in those receiving blood transfusions. This must be critically evaluated since the donor blood was usually obtained from the blood bank. The effect of blood on the clinical symptoms was difficult to evaluate since attacks might cease spontaneously without blood.

On forty-four admissions blood was administered in variable amounts to thirty-four patients. Immediate reactions occurred seventeen times. There was no routine examination of the donor blood for sickling. Usually the reactions consisted of fever, chills and a mild exacerbation of symptoms. Eight reactions were serious; three patients expired within thirty-six hours after the administration of blood. There was a marked increase in the size of the liver, with bilirubinuria, albuminuria and uremia in two of those who expired. The third patient had marked exacerbation of low back pains and he expired within three hours. At the time of the transfusion he was asymptomatic and was ready for discharge from the hospital. In one of the two patients with jaundice a spectroscopic examination for plasma hemoglobin increase was negative. In one severe jaundice developed, the patient did not expire and a subsequent liter of blood was administered without reaction.

Eight bone marrow studies were obtained on cases of sickle cell anemia. All revealed accelerated erythrocytogenesis. Platelet counts, bleeding, clotting and clot retrac-

TABLE III

HEMATOLOGY

Case	Admission				Discharge				Hospital Days	Severity Grades I to IV	Blood Received (cc.)
	Hemoglobin (gm. %)	Red Blood Cells (millions)	White Blood Cells	Reticulocytes (%)	Hemoglobin (gm. %)	Red Blood Cells (millions)	White Blood Cells	Reticulocytes (%)			
1	3	1.16	23,000		6.5	2.71	12,400		17	II	500
2	7.5	2.25	6,600	5	7	2.30	17,700	8.6	18	II	500
3*	4.5	1.23	10,400	35	4.75	1.33	13,600		4	IV	500
4	6.0	1.81	29,000	35	8.5	2.63	16,600		30	III	500
	8.0	2.93	41,400	13.3	8.2	2.26	10,050		34	IV	500
	9	2.82	8,700	17.0	8.5	2.50	14,300	28	10	I	
5	6.5	1.87	15,000	19	9.0	3.38	8,850	5.6	23	IV	3,000
6	6.7	2.36	21,500	10	7.7	3.06	16,000		21	IV	500
	6.5	2.71	11,000	12	8.0	2.80	10,000		17	I	
	7.5	2.89	10,500	18	8	3.04	12,800		9	I	1,000
	8.0	2.58	4,400	15	7.5	2.59	13,600	9.7	14	II	
7	4.0	1.52	48,000	29	7.2	2.60		7.3	42	IV	1,250
	7.5	2.44	14,900		11	3.49	16,250		30	IV	1,200
8	6	2.02	17,200	7	8.2	3.74			27	II	1,000
9	8.3	2.77	16,000	3	10	4.31			31	I	1,000
10	5.25	1.66	14,600		5.7	1.51			30	III	
11	9.0	2.83	14,400	18	8.3	3.11	25,000		39	III	500
12	8.5	3.06	28,000	1.6	8.5	2.83	18,000		35	IV	1,250
	7.7	2.08	10,800		7.7	2.80			11	II	500
13		2.23	21,000		6.8	2.42	11,300		9	III	
	5.0	1.79	8,900		7.8	2.86	7,150		8	III	500
	6.0	2.01			11	3.63				III	
14	5.4	1.70	23,000	15.9	10	3.61	4,000		45	IV	
15	7.5	2.47	16,200	7	7	2.35	16,000		30	IV	1,500
	8.0	2.51			6.5	2.64			78	IV	1,000
	7.5	2.79	14,500	4.7	7.0	2.7	23,000	16.3	22	II	
16	8.0	2.49	16,300		7.0	2.76	15,000		11	II	
	6.2	1.66	21,000		6.7	2.06			11	I	500
	8	2.87	12,000	17	8.5	3.00	11,000		23	III	
	6	2.13	14,000	2.7	7.5	2.58	12,000	6.9	23	II	
	7	2.12	13,300	9.1	7.7	2.60			10	II	500
	6.2	2.50	19,000		8.5	2.96	10,000		15	II	1,000
17	6.5	2.50	6,500	15.3	8.0	3.20	8,400	15.9	13	III	
	7.5	2.53	10,700	7.5	8.5	3.21	11,900		10	II	1,000
	7.5	2.87	12,400	18.8	8	2.35	16,000		8	I	500
18	5.2	1.9	13,000	36	7.0	3.42			12	II	500
19*	5.75	2.27	18,000	17.6	6.0	1.62	13,500	6.2	10	IV	1,500
20*	6.8	2.80	21,000	9.2	8.5	3.13	7,400		20	IV	
21	8.0	2.99	27,000		7.5	2.84	18,000		27	III	1,000
	7.5	2.55	13,000	17.4	7.5	2.80	12,750		15	I	500
22	7.0	2.26	22,000		7.5	2.02	13,000		15	II	
23	8.0	2.64	13,500	6.8	6.4	2.70		5.0	41	III	500
24	6.2	2.34	10,500		7.25	2.80	13,800		34	III	
25*	7.0	2.18	15,500	23.1	6.0	1.90	15,500	29.7	34	IV	
	6.5	1.95	12,000	17	6.5	2.68		6.1	88	IV	7,000
26	7.0	2.39	13,000		10.0	4.01			1		1,000
27	8.5	2.44	10,950	6.0	8.3	2.78	18,000		20	IV	
28	11	3.70		3.8	7	2.44		11.7	48	III	
29	6	1.95	12,700	3.6	7	2.08			45	II	
30	10	3.97			9.5	2.64			6	II	
31	6.5	2.77	7,900	6.6	6.8	2.13		8.6	22	II	1,000

* These patients died during hospitalization.

tion times were obtained on enough patients for a significant report and were not usually abnormal.

Other Laboratory Findings. The basal metabolic rate was determined in three cases and was elevated above the accepted normal in all. The maximum determination was 35 plus. Serum phosphorus and calcium determinations in five cases were not significant. Acid phosphatase was at a normal level in one determination. The carbon dioxide combining power determination was obtained in nine patients and revealed a slight but significant decrease in eight cases. However, because of some technical difficulties previously noted with this test the results in our series are not emphasized and require further and more accurate study. Sodium and potassium levels were obtained by the flame photometric method[9] in two cases and were not significantly abnormal.

Additional Observations. Steady employment was not usually maintained by this group of patients. Frequency of attacks, weakness and easy fatigability prevented gainful labor. Average hospitalization for the group was twenty-five days. The maximum period of hospitalization for any one patient was 157 days which covered a total of ten admissions. This does not include numerous attacks for which hospitalization was not required.

Five patients in this series have had pregnancies. One patient, age forty-one, has had seven children without mishap. Another patient has had two children. This latter patient had significant lowering of the erythrocyte count during each pregnancy, for which frequent blood transfusions were required. Two other patients in this group have had successful pregnancies. One patient had a miscarriage during an active phase of the disease.

Seven patients in this series are known to have expired. The average age of death was 22.7 years. In two patients a severe hepatorenal syndrome developed after blood transfusions and they died within thirty-six hours. Another patient died with marked exacerbation of symptoms within three hours after a blood transfusion. The immediate cause of death in two of these cases was not known, the others died during active phases of the disease. The whereabouts of twenty-four of these patients is known; the others have disappeared.

COMMENTS

In this report emphasis has been placed on the clinical evidence of organic dysfunction. A thorough search of the records revealed significant data which, unfortunately, were not organized for a detailed study of functional activity. Even with organized studies any reports of isolated organic function must be critically evaluated. A state of chronic oxygen want exists, and all organs must be affected even during the quiescent phase of the disease. At the time of the crisis various parts of the body may become the site of severe ischemia and functional activity of the part may become severely altered. It appears, however, that recuperative powers may be adequate, and following the crisis there is usually a return to normal function under standard conditions for this disease. A previous report suggests that functional reserve may also be effective to compensate for any unusual stress.[10]

In this series previous splenectomy had no effect upon the course of the disease. The liver, however, offers opportunity for more detailed study. The increased strain upon the organ, particularly its excretory function, should theoretically give rise to more severe chronic changes. Although deaths were noted in this series with evident hepatic failure, the recuperative powers were usually effective and acute episodes with demonstrable liver damage were followed in short periods by adequate functional activity of the organ. It appears that liver damage during severe crises was usually hepatocellular and cholangiolar, although the theoretical importance of the reticulo-endothelial system, particularly in the hemolytic anemias, suggests need for a thorough study of activity of the Kupffer cells.

The association of pneumonia with sickle cell disease is not usually stressed. The

frequency of pulmonary infections in this series is high. Routine examination of the sputa did not reveal a specific etiologic agent in any of the cases, and it is questionable whether the pneumonia was a part of the crises or whether the infection predisposed to the crises. It is interesting that patients often gave a history of upper respiratory infection previous to the acute onset of pneumonia and crises. In one case the patient entered the hospital with only the signs and symptoms of pneumonia. Two days later he had a typical crisis with marked hepatic enlargement, high elevated direct-reacting bilirubin and joint pains.

The heart findings in sickle cell anemia have been recently reviewed.[11] In this series evidence is presented which indicates that the changes may be only temporary and variable and that the T wave changes suggestive of ischemia may return to the usual upright position. Only two patients in this series exhibited definite severe cardiac failure. One of these had auricular fibrillation and was believed to have associated rheumatic heart disease; the other, the oldest in the series, had associated hypertension and probable nephrosclerosis.

The kidneys likewise present need for further and more detailed study. The fixed specific gravity of the urine has been previously noted.[1] In this series children as well as adults revealed this feature and it is surprising that more cases of progressive renal damage were not seen. Three cases observed with marked urea retention had associated acute hepatic involvement and suggested a hepatorenal syndrome.

A site of constant hyperfunction is the bone marrow. Each marrow study revealed accelerated erythrocytogenesis. The life span of the erythrocyte in this disease is considerably shortened,[12,13] and a basic defect is believed present in the hemoglobin molecule.[14] The bizarre shape, theoretically, results in mechanical hemolysis as it circulates through the finer vascular radicles. It appears that this is more or less a constant feature and that other factors are needed to precipitate the true picture of a crisis. From the results presented in this communication restoration of the erythrocyte count to a normal or near normal level is not needed to terminate the crisis. In fact, several cases presented no change or a decreased erythrocyte count after disappearance of symptoms. It should be emphasized that changes in blood and plasma volumes must be considered before accurate erythrocyte counts are acceptable.

Reactions to blood transfusions are more frequent and severe than usually occur. The reason for this is not known; however, the possibility of a previous formation of subagglutinins, the result of frequent transfusions, must be considered. Contrary to this belief is the occasional occurrence of reactions in patients in this series who were given blood for the first time. The routine administration of blood also appears useless except in cases in which the severity of the attack and shock demand immediate therapy. Small transfusions are of little benefit and massive transfusions at the most can be of value for only a limited time.

SUMMARY

The clinical manifestations of fifty-four patients with sickle cell anemia admitted to the charity hospitals of this area during the past ten years are presented. Emphasis has been placed on evidence of organic dysfunction.

The presence of the direct-reacting bilirubin suggests hepatic involvement. The meager function studies presented must be critically evaluated, but if accepted indicate a return to normal function after the severe crises. Changes in the heart and kidneys, as well as evidence of pulmonary involvement, are also stressed.

Hematologic studies indicate continued hyperactivity of the bone marrow and a disappearance of symptoms of this disease without persistent elevation of the erythrocyte count. The frequency of blood transfusion reactions and the lack of evidence of prolonged benefit to the total circulating erythrocyte count should condemn routine administrations of blood except in those

cases of severe attacks in which heroic methods are needed.

The morbidity and mortality rates in this disease, as well as the ignorance of the basic defect of the erythrocyte, suggest further research in this field.

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REFERENCES

1. Wintrobe, Maxwell M. Clinical Hematology, pp. 398–414. Philadelphia, 1942. Lea and Febiger.
2. Grover, Victor. The clinical manifestations of sickle cell anemia. *Ann. Int. Med.*, 26: 843–851, 1947.
3. Winsor, T. and Burch, G. E. Diagnostic physiocochemical blood tests in sickle cell anemia. *Am. J. M. Sc.*, 207: 152–160, 1944.
4. Sherman, I. J. The sickling phenomenon, with special reference to the differentiation of sickle cell anemia from the sickle cell trait. *Bull. Johns Hopkins Hosp.*, 67: 309–324, 1940.
5. Sharp, E. A. and Vonder Heide, E. C. Eunuchoid habitus associated with sickle cell anemia and the sickling trait. *J. Clin. Endocrinol.*, 4: 505–510, 1944.
6. Watson, C. J. and Hoffbauer, F. W. Liver function in hepatitis. *Ann. Int. Med.*, 26: 813–842, 1947.
7. Legant, Omar and Ball, Robert P. Sickle-cell anemia in adults: roentgenographic findings. *Radiology*, 51: 665–675, 1948.
8. Macht, Stanley H. and Roman, Paul W. The radiologic changes in sickle-cell anemia. *Radiology*, 51: 665–675, 1948.
9. Mosher, Robert E., Boyle, A. J., Bird, Edward J., Jacobson, S. D., Batchelor, Thomas M., Iseri, Lloyd T. and Myers, Gordon B. The use of flame photometry for the quantitative determination of sodium and potassium in plasma and urine. *Am. J. Clin. Path.*, 19: 461–470, 1949.
10. Henderson, A. B. and Thornell, H. E. Observations on the effect of lowered oxygen tension on sicklemia and sickle cell anemia among military flying personnel. *J. Lab. & Clin. Med.*, 31: 769–776, 1946.
11. Winsor, T. and Burch, G. E. Electrocardiogram and cardiac state in active sickle cell anemia. *Am. Heart J.*, 29: 685, 1945.
12. Singer, Karl, Robin, Sidney, King, Joseph and Jefferson, Ronald N. The life span of the sickle cell and the pathogenesis of sickle cell anemia. *J. Lab. & Clin. Med.*, 33: 975–984, 1948.
13. Callender, Shelia T. E., Nickel, James F. and Moore, Carl V. Sickle cell disease: studied by measuring the survival of transfused red blood cells. *J. Lab. & Clin. Med.*, 34: 90–104, 1949.
14. Pauling, L., Itano, H., Singer, S. J. and Wells, I. C. Sickle cell anemia, a molecular disease. *Science*, 110: 543–548, 1949.

Seminars on Renal Physiology

Renal Function in Renal Diseases*

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According to current concepts of renal physiology urine is elaborated from a filtrate of plasma by the direct activity of renal tubular cells. Physical separation of the formed elements and macromolecules from the water and solutes of the blood takes place by filtration across the glomerular capillary membrane under the hydrostatic pressure of the blood. This process is limited by the oncotic pressure of the plasma proteins, by the diffusibility of the various solutes and by the intrarenal pressures as well as by the character of the membrane. The filtrate thus formed pours down the tubules where most of it is reabsorbed and returns to the circulation. The remainder is transformed by selective reabsorption and excretion of solutes and water before it appears in the bladder as urine. The composition of the urine reflects the processes to which the filtrate has been subjected on its way to the bladder and abnormal function at different stages may be discerned in studies of urinary excretion. The clearance technics provide a means by which renal blood flow, glomerular filtration and tubular functions may be evaluated in quantitative terms. Moreover, venous catheterization has permitted direct sampling of renal venous blood and determination of the renal extraction of various substances. The discussion that follows will be limited to a consideration of the changes in renal physiology disclosed by these methods in the bilateral non-suppurative nephropathies, including the nephritides, nephroses, nephroscleroses and certain congenital disorders.§

METHODS

The subjects of these studies were selected from among the patients encountered on the wards of the Massachusetts Memorial Hospital, Boston, and the Presbyterian Hospital, New York. Selection depended in every case upon a clearcut diagnosis based upon clinical findings and laboratory investigation. Followup over a period of several years in the outpatient departments of these institutions permitted further appraisal and confirmation of the initial diagnoses. Postmortem examinations were made in only four of the twenty known to have died since study and in each the clinical opinion was sustained. It is unfortunate that a better correlation between clinical, physiologic and pathologic data is not possible but this failing seems almost unavoidable. However, the lesions observed at necropsy may have little bearing upon the earlier functional data. Extensive studies of renal pathology during the last half century have provided widely accepted correlations between certain sharply defined clinical and pathologic entities. We have sought to take advantage of this fact by making a study of renal function only in clinical states in which the anatomic changes are known. Thus an indirect correlation between the physiology and pathology of the kidney may be achieved. No

§ Preliminary reports of some of these data have appeared elsewhere.[1,2]

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attempt has been made to analyze the data presented here by statistical methods because the groups of patients investigated are inherently heterogeneous. It is not yet possible to select patients at any single point in the disease process and it has been deemed preferable to present the data as obtained in relation to the mean normal values. For similar reasons correction to a uniform surface area has been eschewed.

The renal blood flow was determined on the basis of the p-aminohippurate (PAH) clearances corrected by the hematocrit and, in most cases, by renal PAH extraction. Glomerular filtration was measured by the inulin or mannitol clearances and tubular function was assessed principally in terms of maximal tubular PAH (Tm_{PAH}) excretion.[3] These methods were supplemented by careful clinical and laboratory studies. As noted in subsequent sections, electrolyte, nitrogen and water excretion were measured in a few individuals in connection with the clearance procedures or in balance studies carried out on the Metabolism Service of the Presbyterian Hospital.

Measurements of clearances and transfer maxima (Tm) were made on all subjects in recumbency in the fasting, resting state shortly after awakening in the morning. In the majority, 1,000 to 1,500 ml. of water were ingested during the hour prior to study in order to assure adequate urine flow. A multiholed rubber catheter was placed in the bladder, using surfacaine jelly®* to allay local irritation and discomfort. The bladder was emptied by manual expression, washed out with sterile distilled water or isotonic saline solution, and the urine and "washout" thus obtained discarded. Urine was then collected over a ten-minute period, the bladder washed out with a measured volume of sterile distilled water or isotonic saline, and the total volume carefully measured and saved as a blank. An infusion of inulin or mannitol and PAH† made up in sterile isotonic saline or glucose (5 per cent) solution in appropriate concentrations to maintain plasma levels of inulin at about 20 mg. per cent, mannitol at 100 mg. per cent and PAH at 1 mg. per cent, when delivered intravenously at 4 ml. per minute, was started after administration of priming doses of these substances. As a rule priming doses of PAH (25 per cent) consisted of 1 cc. to obtain plasma levels consonant with clearance measurements and 20 to 50 cc. for Tm measurements; mannitol (25 per cent) and inulin (10 per cent) were usually given in 30 ml. amounts. Rapid administration (faster than 5 ml. per minute) of large volumes of concentrated PAH solution usually gave rise to unpleasant symptoms of hot flushing, abdominal cramps, nausea and rarely vomiting or diarrhea. The infusion was administered intravenously at a constant rate through a brachial vein by gravity, using a tunnel clamp and calibrated Murphy drip, or by a calibrated pump. After a period of approximately thirty minutes to permit equilibration of the plasma concentrations the bladder was emptied, washed out and the urine discarded. A sample of blood was taken from a brachial vein in the opposite arm and urine carefully collected and measured with the wash-out at about ten-minute intervals for three or more periods. Venous blood was sampled at about forty-minute intervals. The values for clearances and Tm were calculated in the usual manner, using figures for plasma concentrations obtained by interpolation from curves of observed concentrations plotted semi-logarithmically against time.

Sodium p-aminohippurate and inulin were determined colorimetrically in diluted aliquots of urine and filtrates of cadmium sulfate precipitated plasma samples[4] by the methods of Smith et al.[5] and Harrison,[6] respectively. Recoveries of PAH from both urine and plasma were uniformly good, ranging from 96 to 104 per cent on various occasions. Inulin recoveries were less complete, ranging from 92 to 96 per cent. The inulin method is often erratic and must be carefully controlled. Mannitol was determined in diluted urine and plasma filtrates by iodometric titration according to the method of Smith et al.[7] modified in accord with the suggestions of Barker and Clark.[8] Almost a third of the determinations were made before the latter pointed out the interference of PAH with mannitol determination but no effort has been made to correct these values because the error appears to be small except in measuring Tm_{PAH}. In this case averaged control figures for mannitol clearances were used in calculating Tm when PAH interference with mannitol values appeared. Recoveries of mannitol from urine and plasma averaged 89 per cent and

* Supplied through the courtesy of Eli Lilly and Company, Indianapolis, Ind.

† We are indebted to Dr. W. Boger and the Medical Research Division of Sharp and Dohme, Inc., Philadelphia, Pa., for a generous supply of mannitol and sodium p-aminohippurate.

92 per cent, respectively. In some instances diodrast clearances or Tm were determined to measure renal plasma flow or tubular excretory activity, respectively, and in others maximal glucose reabsorptive capacity (Tm_g) was measured. Diodrast was determined in diluted urine and plasma filtrates by iodometric titration according to the method of Alpert.[9] The Nelson[10] method for glucose analysis was employed. Arterial blood samples were used throughout in following glucose plasma concentrations. Plasma concentrations for diodrast, inulin and mannitol must be corrected by a value for apparent levels of these materials in venous blood obtained before beginning the test. These values for plasma blank are variable and may be large and significant in the presence of renal disease.

In most subjects considered in this paper PAH extraction was measured in order to obtain an accurate estimation of renal blood flow. The use of the PAH or diodrast clearances as measures of renal plasma flow requires the assumption that all or almost all of these materials is removed from the blood perfusing the kidneys. This assumption has been shown[2] to be valid for normal human subjects since PAH extraction by the kidney in twenty-five subjects was found to average 93.5 per cent, ranging between 89 and 100 per cent, provided the plasma level does not exceed 3 or 4 mg. per cent. Since PAH and diodrast clearances are approximately equal, it may be presumed that diodrast extraction is equally high. Direct determination of diodrast extraction in four normal subjects at the beginning of these studies revealed values ranging from 65 to 85 per cent. It was believed that these low values could be accounted for by shift of diodrast from the erythrocytes into the plasma in the time that passed before cells and plasma were separated. However, Josephson and his colleagues[11] believe this does not wholly explain the phenomenon. White[12] has claimed that considerable diodrast must be cleared from the cells and it is possible that transfer occurs within the renal vessels. This difficulty does not arise in the case of PAH because it does not enter the erythrocyte in man. In any case the agreement between diodrast and PAH clearances appears to validate the use of the former for measuring renal plasma flow. In the presence of renal disease it may be presumed that PAH and diodrast extraction is impaired and that their clearances are no longer useful for this purpose. In the studies reported here we have spoken of renal blood flow only when figures for extraction were available or when otherwise properly qualified. The clearance value may be corrected by dividing it by the extraction per ml. of plasma flowing through the kidney to yield a figure for true plasma flow. The blood flow may then be calculated from this value and the hematocrit.

Renal venous blood samples were obtained by passing an extra length radio-opaque ureteral catheter into the right renal vein by way of a brachial vein, the superior vena cava, right auricle and inferior vena cava under fluoroscopic control.[13] Metycaine* (2 per cent) was used for inducing local anesthesia in making the cutdown to the vein for insertion of the catheter. In about one-third of the cases procaine (2 per cent) was used for this purpose. Procaine may interfere with PAH determination but it was found that in the amounts used not enough drug entered the circulation to produce detectable concentrations in peripheral venous blood. Nonetheless, when metycaine became available the use of procaine was abandoned. The difference between values for PAH concentrations in simultaneous samples of peripheral and renal venous blood divided by the peripheral venous concentration yields a value for renal extraction. Determination of PAH in the renal venous blood is often difficult because the concentration is so low. For this reason standard was added to the filtrate and the value obtained by difference.

The use of the PAH extraction and clearance method for the purpose of accurately estimating renal blood flow involves the assumption that PAH is extracted by renal tubule cells and excreted forthwith by the kidney without further alteration. The lymph flow from the kidney appears to be small[14] and it seems unlikely that any significant amount is lost by this route. It is possible that acetylation of PAH takes place in the kidney and that PAH appears in the renal venous blood in the undetected acetylated form (PAAH). Determination of PAAH in renal venous blood by a modification of Smith's method[5] failed to reveal any significant concentration. In ten of twenty patients PAAH extraction was approximately equal to PAH extraction determined simultaneously. In the remainder it was low (10 to 30 per cent) and in three the level of PAAH in renal venous blood was somewhat higher than the level in peripheral venous

* Supplied through the courtesy of Eli Lilly and Company, Indianapolis, Ind.

blood. In no instance was the PAAH in the renal venous blood higher than 0.2 mg. per cent. It may be concluded that insufficient acetylation of PAH occurs in the kidney to interfere materially with measurement of its extraction. It seems reasonable, therefore, to accept the clearance and extraction method as a valid means of estimating renal blood flow.

Berger and his colleagues[15] have found that the mannitol clearance is lower than inulin clearance by 10 per cent on the average, possibly as a result of back-diffusion of the substance during its passage down the tubule. A similar discrepancy has been noted in this laboratory[16] but the discrepancy does not appear to be increased by renal disease. Since the error thus introduced appears to be small in terms of the other possible errors involved in employing these substances to measure filtration rate under the circumstances of disease, we have continued to use the inulin and mannitol clearances interchangeably. Back-diffusion of inulin or mannitol may possibly occur when the kidneys are severely damaged, as suggested by Bobey[17] and others,[18] but there seems to be little doubt that these clearances testify to the relative if not the absolute values for glomerular filtration rate.

Tubular functions may be examined by many methods. All require evaluation of urinary excretion in terms of glomerular filtration and are therefore only as accurate as the measurement of filtration. We have chosen to characterize tubular activity in the present study chiefly by measuring maximal PAH excretion, first because this function could be compared with PAH extraction in appraising the extent of exclusion of tissue from effective perfusion by disease, and second because the large tubular excretion of this substance minimizes inaccuracies introduced by errors in measuring filtration. It should be noted that some of the PAH of plasma is bound by plasma proteins and is not available for filtration. This fact is taken into account in calculation of Tm through the use of a standard correction factor.[5] When the plasma proteins are reduced, as in the nephrotic syndrome or in malignant nephrosclerosis, less PAH is bound and uncorrected values for Tm may be somewhat too high. In the present study satisfactory determination of plasma protein concentration was not always possible and it was decided therefore to use the figures calculated in the usual way. This may have introduced error in certain cases which will be noted in the appropriate sections. In connection with certain related problems of body water and electrolyte disturbances consequent upon renal dysfunction attempts have been made to assess tubular handling of water, sodium and potassium. An internal lithium standard flame photometer was employed to measure concentrations of sodium and potassium in plasma and urine. Tubular reabsorptive activity was also evaluated on several occasions in terms of maximal glucose reabsorption.

INTERPRETATION OF RESULTS

Since the PAH and diodrast clearances measure the amount of plasma virtually cleared of these substances, even when renal extraction is impaired, they yield minimal, if not absolute, values for renal plasma flow. Smith [9] has suggested use of the term "effective renal plasma flow" (ERPF) as a satisfactory equivalent expression for diodrast or PAH clearances. He has pointed out the probability that the tissues engaged in the process of extraction contribute to the measured value for diodrast or PAH Tm which is roughly equivalent to the mass of active tissue. Hence, expression of the clearance in terms of the value for Tm; i.e., as the ratio between clearance and Tm, should provide a measure of the blood flow per unit mass of excretory cells. Owing to depression of extraction by overloading at even low PAH plasma levels, the PAH clearance may fail to measure blood perfusing damaged tissue that contributes to Tm. For this reason the ratio between true renal blood flow (determined by the clearance and extraction method) and Tm_{PAH} appears to be a more reliable means of estimating relative perfusion; i.e., hyperemia (high ratio) or ischemia (low ratio) of active tubules. In like manner the ratio between filtration rate (GFR) and Tm_{PAH} indicates glomerular activity in terms of operative nephrons; a high value denoting hyperfiltration in residual active units; a low value, hypofiltration. The filtration fraction (F.F.) or the percentage of plasma flow subjected to filtration (GFR/ERPF) is of value in assessing hemodynamic adjustments of afferent and efferent arterioles

only when all of the blood passing through the kidney traverses glomeruli. The presence of glomerular by-passes in advanced renal disease[20] calls for caution in the interpretation of changes in this value.

Interpretation of the alterations in renal function during disease must also make allowances for homeostatic adjustments. The renal vasculature appears to participate actively in systemic circulatory responses to stress. All these changes appear to be related to the change in effective circulating blood volume. Peripheral circulatory collapse or shock resulting from many causes evokes a marked intrarenal vasoconstriction that serves to sustain arterial pressure and to supplement the cardiac output by diverting blood to other tissues. A similar response has been observed in severe anemia.[21] Figure 1 summarizes the findings in fifteen individuals with anemia due to various causes. The clearance values were not much depressed but whole blood flow was decreased by 40 per cent on the average. In this manner adequate plasma was available for filtration and urine formation. The vasoconstriction implicit in this change was completely reversible. In contrast, hyperemia of the kidney develops during the pyrogenic reaction[22] and increased renal blood flow has been encountered in patients with secondary polycythemia.[23] Studies of five individuals with polycythemia vera presented in Table 1 reveal high values for effective renal blood flow in four.

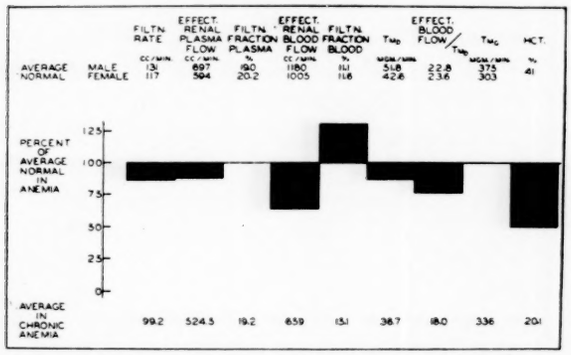

FIG. 1. Changes in renal function during chronic anemia; the average values for glomerular filtration rate, effective renal plasma flow, renal blood flow and tubular transfer maxima for glucose (Tm_g) and diodrast (Tm_D) in fifteen patients with chronic anemia from various causes, are expressed in terms of average normal values[86] in this figure. The clearances fell moderately and to about the same extent, but renal blood flow was reduced by almost 50 per cent largely as a result of the fall in hematocrit (Hct). The plasma filtration fraction (GFR/RPF) thus did not change, whereas the whole blood filtration fraction (GFR/RBF) increased, presumably indicating predominantly efferent arteriolar vasoconstriction. Diodrast Tm decreased and glucose Tm remained within normal limits. All values were corrected to an average body surface of 1.73 M^2.

THE NEPHRITIDES

The bilateral inflammatory diseases of the kidney may be divided for purposes of discussion into two major groups—glomerulonephritis and pyelonephritis. Glomerulonephritis is characterized chiefly at the onset by glomerular lesions and pyelonephritis by tubular lesions. In both, progression ultimately results in involvement of the total parenchyma with destruction of tissue fibrosis. As a result the renal vasculation may undergo extensive transformation. The end-stage of both disorders may thus be indistinguishable on pathologic grounds and it is not surprising that function should follow suit and characteristic differences vanish. The patterns of dysfunction peculiar to these disorders and their several stages conform to expectation grounded upon the anatomic changes.

Glomerulonephritis

The functional disturbances of diffuse glomerulonephritis have been subjected to investigation by many workers.[24–28] This disease has a long and complicated course and may be considered as a series of connected but discrete disorders that grade imperceptibly into one another, viz., the acute, nephrotic and terminal phases.

Acute Phase. According to Bell[29] the glomerular capillaries are progressively obstructed during acute diffuse glomerulonephritis by proliferation of endothelium or by epithelial crescents compressing capillary loops. This plugging of capillaries obviously reduces the filtering surface in any individual glomerulus. Hence it is not surprising that Earle et al.[24] and many others have

found the filtration rate uniformly depressed. Likewise, in eleven of the sixteen patients with acute nephritis (Table II) studied in the course of this investigation the glomerular filtration rate as measured by mannitol or inulin clearance was significantly reduced. values for renal blood flow that were within or in excess of the normal range. In view of the demonstrable obstructive vascular lesion in the kidney, with exclusion of blood from many parts of the renal vascular bed, this finding must indicate a rather marked

TABLE I
RENAL FUNCTION IN POLYCYTHEMIA VERA*

Subject	S.A.	Sex	Age	Hematocrit %	GFR ml./min.	ERPF ml./min.	F.F. %	ERBF ml./min.	Tm_D mg./min.
B. W.	1.68	M	62	60	121	688	18	1720	36
E. P.	1.58	M	53	44	104	923	11	1565	93
E. L.	1.76	M	50	67	53	397	15	1200	..
M. H.	1.76	F	62	51	45	362	13	740	38
J. B.	1.86	M	50	75	70	424	17	1695	42

* All clearance values are averages of two or more determinations. The glomerular filtration rate (GFR) was measured by the inulin (B. W. and E. P.) and mannitol clearances, effective renal plasma flow (ERPF) by diodrast and PAH (E. L.) clearances. The effective renal blood flow (ERBF) was calculated from the ERPF and hematocrit. Maximal tubular excretion of diodrast (Tm_D) was measured in all except E. L. These figures have not been corrected for differences in body surface (S.A.). Diagnoses were well established in every case presented here and confirmed by prolonged follow-up. Treatment by removal of blood had been started in all except J. B., effective reductions in hematocrit were noted only in E. P. and M. H. In all except M. H. therapeutic bleeding had not been carried out for several weeks and it is possible that the relatively low clearance values in M. H. are explicable on this basis.

As Black[26] has pointed out it seems unlikely that the thickening of the basement membrane plays a very important role in causing this change since the characteristic proteinuria and hematuria indicate that the permeability of the remaining filtering surfaces is increased rather than diminished.

Black[26] suggests that vasoconstriction, particularly of the afferent arteriole, may be an important factor in reducing the head of filtration pressure within glomerular capillaries and so in decreasing filtration. This view is supported by the fact that the PAH clearance usually decreases, occasionally to a marked degree, though usually not to the same extent as filtration. Moreover, the rapid reversibility of the filtration defect in association with augmented PAH clearance seems to be more readily explained by relaxation of constricted vessels. However, studies of PAH extraction (Table II) have revealed that measurement of renal plasma flow by the PAH clearance may be grossly in error in this condition. Correction of the clearance value by the observed extractions (ranging from 69 to 83 per cent) yielded hyperemia of perfused tissue. And since the blood pressure was not invariably much increased (F. C., M. C. and A. S.—Table II, for example) the augmented blood flow must imply active vasodilatation of afferent arterioles. The pattern of change which now emerges conforms with that seen in the pyrogenic reaction[22] and is in harmony with the view that glomerulonephritis is an inflammatory disease of the kidney. Nonetheless, it is difficult to exclude vasoconstriction altogether in certain cases. In M. B. and L. L. (Table II), for example, in whom PAH extraction was unfortunately not measured, the clearances of PAH and diodrast, respectively, were so markedly depressed early in the disorder that it is hard to believe that defective extraction alone accounts for the observed change. Renal vasoconstriction in these patients is probably attributable to impending or clearing congestive heart failure rather than to the kidney disease *per se*.

As the following study reveals, the diseased kidney appears to respond to stress of various types like the normal. Figure 2 illustrates the

TABLE II

RENAL FUNCTION IN ACUTE DIFFUSE GLOMERULONEPHRITIS*

Subject	S.A.	Sex	Age	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} ml./min.	RBF ml./min.	Tm_{PAH} mg./min.	GFR/Tm_{PAH} ml./mg.	RBF/Tm_{PAH} ml./mg.	Azotemia	Edema	BP mm. Hg	Estimated Days of Disease
L. L.	1.66	M	16	46	264	19	...	....	..	....	....	Y	Y	130/88	18
				56	488	12	...	....	..	....	....	N	N	124/98	34
				69	440	16	...	....	..	....	....	N	N	114/84	62
				111	687	16	...	....	..	....	....	N	N	108/80	87
M. B.	2.08	F	52	17	63	28	...	....	..	....	....	Y	Y	164/74	7
				60	313	19	...	....	40	1.49	....	Y	Y	156/95	11
				85	406	21	...	....	53	1.59	....	N	Y	144/84	20
F. C.	1.54	M	11	48	363	13	...	....	29	1.63	....	Y	Y	140/75	10
				35	436	8	83	965	30	1.17	32.2	Y	Y	124/80	20
M. C.	1.76	M	39	...	505	..	77	1120	..	....	....	Y	Y	150/90	24
J. S.	0.85	F	6	14	113	12	...	....	8	1.68	....	Y	Y	172/120	10
I. A.	1.53	F	25	28	327	9	47	932	..	....	....	Y	Y	145/95	39
M. S.	1.75	M	47	67	653	10	76	1278	81	0.83	15.8	Y	Y	196/104	9
G. M.	0.85	F	7	34	251	14	...	....	15	2.21	....	Y	Y	120/80	14
E. S.	1.68	F	14	41	405	10	80	824	..	....	....	N	Y	135/105	20
A. S.	1.58	F	37	67	598	11	83	1226	54	1.23	22.7	Y	Y	150/80	26
L. P.	1.64	M	52	90	500	18	69	1021	60	1.50	17.0	N	N	234/138	49
M. K.	1.62	M	52	64	475	13	...	....	..	....	....	N	N	178/68	41
B. S.	2.24	M	44	23	226	10	...	....	..	....	....	N	N	120/66	112
A. W.	1.90	M	45	48	357	13	...	....	..	....	....	N	N	142/94	98
H. C.	2.04	M	47	157	1320	12	100	2345	72	2.18	32.6	N	N	100/60	64
T. B.	1.03	M	15	63	403	15	94	757	..	....	....	N	N	108/72	16
Mean Normal [2,86,100]	1.73	M	..	131	697	19	93	1340	78	1.68	17.2	..	..	.....	..
	1.73	F	..	117	594	20	93	1180	78	1.50	15.2	..	..	.....	..

* All values for glomerular filtration rate (GFR), effective renal plasma flow (ERPF—diodrast or PAH clearance), filtration fraction (F.F.—GFR/ERPF) and maximal tubular excretion of PAH (Tm_{PAH}) are averages of two or more determinations. Values for renal blood flow (RBF) and ratios between filtration (GFR/Tm_{PAH}) or renal blood flow (RBF/Tm_{PAH}) and Tm_{PAH} are calculated from these figures. The renal extraction of PAH (E_{PAH}) was determined simultaneously with measurement of PAH clearances. The presence (Y) or absence (N) of azotemia and edema are noted without any attempt to provide a quantitative figure. These subjects are arranged in order of the clinical severity of the disease at the time of the initial study. The diagnosis seemed clearcut in each, though in one (F. C.) the disorder had its onset with the nephrotic syndrome and hematuria and subsequently entered the typical chronic stage.

renal functional changes observed in three patients with acute nephritis studied before and during assumption of the upright position. It can be seen that all clearance values fell after the change in the body position, presumably indicating a decrement in glomerular filtration and in renal blood flow. The PAH extraction was not measured in these studies but since PAH clearance decreased in association with a fall in inulin clearance a vasomotor change is more probable than a change in tubular PAH extraction. These alterations are equivalent to those observed in normal subjects on standing[30] and they may be interpreted therefore simply as evidence of a renal vascular adjustment to orthostasis. The decreased blood flow cannot be accounted for by diminished arterial pressure because the blood pressure tended to rise on standing. This adjustment on the part of the renal vasculature may be of benefit in terms of this systemic circulation but is definitely detrimental from the standpoint of renal excretory activity. In each instance the urine became grossly bloody and proteinuria increased. The urine flow fell sharply in association with an even more striking reduction in sodium and potassium output. These changes were greater than the change in glomerular filtration, indicating a relative increment in tubular reabsorption of water and electrolytes. This vascular reactivity in the presence of acute renal disease undoubtedly predisposes to edema formation and nitrogen retention as well as to urinary abnormalities.

The disturbance of filtration in acute nephritis appears to be sufficient to account for azotemia and diminished urea clearance. Whether this change wholly explains retention of water and electrolyte is debatable. A reduction in filtration alone appears to promote excessive tubular reabsorption of water and salt (as in the study portrayed in Figure 2 and in other investigations[31,32] of normal animals and man), possibly because filtration is diminished diffusely in all glomeruli. The resulting slowing of the stream of filtrate down all the tubules prolongs contact with the reabsorptive surface and presumably permits more efficient transfer of water and solutes. It may be postulated that relative augmentation of tubular reabsorption in this manner is important in promoting edema formation in acute nephritis. This view requires less dis-

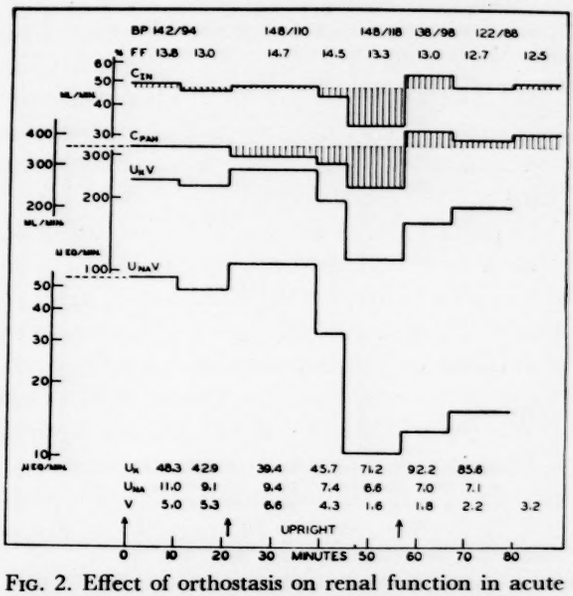

FIG. 2. Effect of orthostasis on renal function in acute diffuse glomerulonephritis; inulin clearance (C_{IN}—glomerular filtration rate) and PAH clearance (C_{PAH}—estimated renal plasma flow) were measured before, during and after tilting patient A. W. (a forty-five year old white male, recovering from typical acute diffuse glomerulonephritis) into the upright position. During orthostasis both clearance values decreased in association with a fall in urine flow (V) and returned to or above the base-line levels on restoration to the recumbent position. The filtration fraction (C_{IN}/C_{PAH}) tended to rise. The urinary output of both sodium ($U_{Na}V$) and potassium (U_KV) ions decreased and tended to remain low. The urinary concentration of sodium ions (U_{Na}) fell, whereas urinary potassium concentration (U_K) rose. The inulin concentration also increased, indicating relatively augmented water reabsorption. During orthostasis the urine became grossly bloody and proteinuria increased. The blood pressure also rose to hypertensive levels. Similar but more marked changes occurred in two other adult males with this disease.

turbance of the tubules than of the glomeruli and is consonant with the known paucity of tubular pathology. Tubular functional abnormalities are also minimal. The excretion of phenolsulphonphthalein (PSP) is frequently normal even in the presence of uremia, and Earle and his associates[24] have found that glomerular filtration may be depressed more than maximal tubular ex-

cretion of diodrast (Tm_D). However, the values for filtration rate and Tm_{PAH} (Table II) were affected almost equally in the present study so that GFR/Tm_{PAH} was not usually greatly depressed but it is possible that Tm_{PAH} was no longer a good measure of total functioning tubular mass under these circumstances. It should be noted that the reductions in Tm_{PAH} noted here and in Tm_D reported by others apparently indicate involvement of tubular as well as glomerular tissue in the pathologic process of acute diffuse glomerulonephritis.

Impaired extraction of PAH is probably related to this disturbance of tubular function rather than to the operation of arteriovenous shunts. The kidneys are engorged with blood at death and there is no anatomic evidence of redistribution of flow. Both PAH clearance and the renal blood flow appear to be relatively large. It may be surmised, therefore, that the reduction in PAH extraction denotes perfusion of a large mass of non-extracting tissue. The reduction in renal oxygen extraction and renal oxygen consumption observed by Cargill and Hickam[33] in acute nephritis conforms with this view.

The clinical course of the acute phase is notably variable. Hematuria, proteinuria, azotemia, hypertension and edema usually appearing abruptly from one to three weeks after an upper respiratory infection mark the typical case. These manifestations vary in severity and appear to depend primarily upon the extent and character of the glomerular disorder. (Table II.) A surprising degree of reversibility is observed. In M. B. and L. L. almost complete return to normal function was achieved within a period of a few weeks. The factors concerned in determining chronicity of the lesion are not demonstrable in the data on function available here and elsewhere. One of the cases reported here (F. C.) began abruptly with the nephrotic syndrome (heavy proteinuria, hypercholesterolemia, hypoproteinemia and edema) in association with moderate hematuria and hypertension. Functionally, this individual could not be differentiated from other patients with acute nephritis but he has shown rapid progression into the chronic terminal phase of the disease. We have encountered at least three other patients with this form of the disorder which resembles the Type II nephritis of Ellis.[34]

The cause of hypertension in acute nephritis is also obscure. No correlation between changes in renal blood flow and the appearance of elevated blood pressure was observed in these studies. Certainly renal ischemia does not seem to be implicated.

Nephrotic Phase. The nephrotic phase of glomerulonephritis usually arises *de novo*, appearing insidiously with proteinuria and moderate edema ultimately verging into the outspoken nephrotic syndrome. Occasionally, it may begin abruptly in or upon the heels of acute nephritis, more commonly it may precede the development of the end stage by months or years. There may be few if any pathologic changes in renal structure or the kidneys may be grossly swollen and deformed by tubular cellular inclusions of fatty or colloid material. Despite these irregularities the position of the nephrotic phase within the pattern of the disease appears to be well established and, in view of its close link to the other stages of glomerulonephritis, cannot reasonably be considered an independent entity.

Tables III and IV reveal how widely renal function may vary in the nephrotic phase despite a superficial uniformity of the clinical manifestations. One of these individuals (H. N.—Table IV) was observed during the course of spontaneous diuresis. In two (J. C. and S. R.—Table IV) the blood pressure was significantly elevated and azotemia was present, indicating coincidence of the nephrotic and terminal phases. The glomerular filtration rate ranged from 14 to 102 ml. per minute and renal blood flow from 709 to 1,380 ml./min. As in acute nephritis the filtration rate was reduced more than effective renal plasma flow or PAH clearance (ERPF) so that the filtration fraction was usually lower than normal. The clinical state was not obviously correlated with any definite degree or pattern of renal dysfunction, except insofar as continuous

TABLE III

RENAL FUNCTION IN NEPHROTIC PHASE OF CHRONIC DIFFUSE GLOMERULONEPHRITIS*

Subject	S.A.	Sex	Age	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} %	RBF ml./min.	Tm_{PAH} mg./min.	GFR/Tm_{PAH} ml./mg.	RBF/Tm_{PAH} ml./mg.
R. B.	2.03	M	17	43	684	8	74	1380	38	1.13	36.3
E. H.	2.09	M	23	45	548	8	98	844	34	1.32	24.8
S. H.	1.61	M	34	50	407	12	76	765	36	1.39	21.2
M. G.	1.58	F	36	58	321	18	74	709	33	1.76	21.4

* Only patients in whom E_{PAH} was determined are included here. Each presented the typical picture of the nephrotic syndrome, without hypertension or azotemia. The diagnosis has been proved in two at autopsy (E. H. and M. G.). S. H. is described at length in Table IV, and R. B. has entered the terminal phase with the appearance of hypertension and uremia complicated by the development of Hodgkin's disease. Abbreviations and values are as noted in Tables I and II; the figures are arranged here in the order of the values for RBF.

TABLE IV

RENAL FUNCTION BEFORE AND AFTER INTRAVENOUS ADMINISTRATION OF CONCENTRATED HUMAN SERUM ALBUMIN*

Subject	Urine Flow ml./min.		GFR ml./min.		ERPF ml./min.		Tm_g mg./min.		Albumin Administered (gm.)
	Before	After	Before	After	Before	After	Before	After	
Normal Controls									
R. F.	5.6	6.4	107	143	770	896	...	...	50
E. S.	4.3	6.6	84	92	526	792	...	...	50
F. B.	2.9	2.3	100	95	653	767	...	...	50
W. H.	3.8	6.8	102	119	592	802	...	...	50
P. H.	7.2	12.4	108	115	562	715	...	...	50
A. G.	5.2	8.6	91	91	480	622	...	...	50
Nephrotic Subjects†									
E. H.	1.3	2.9	35	53	263	290	107	188	25
E. H.	1.5	2.2	45	58	504	557	167	209	25
E. H.	1.6	2.2	22	38	290	342	...	...	50
H. N.	13.2	6.9	98	132	679	569	317	468	50
G. T.	5.0	15.0	90	128	600	756	...	...	50
T. D.	2.4	5.7	86	79	421	524	...	...	50
M. De.	3.8	6.6	67	78	560	695	...	...	50
M. B.	4.0	7.8	45	49	242	315	...	...	50
R. B.	1.4	1.6	29	31	200	277	...	...	50
J. C.	3.4	4.4	16	19	...	...	12	11	50
S. R.	4.8	6.5	18	20	51	59	...	...	50

* All values before administration of albumin are averages of two or more determinations, all after albumin are single determinations showing the maximal change. Abbreviations as noted in Tables I and II.

† Each of these subjects presented all the manifestations of the nephrotic syndrome, apparently on the basis of chronic diffuse glomerulonephritis. Hodgkin's disease was a causative factor in the case of T. D. Hypertension and nitrogen retention had appeared in J. C. and S. R.

excessive proteinuria permitted loss of plasma proteins and impaired filtration resulted in retention of nitrogen.

It is extremely difficult to evaluate hemodynamic alterations on the basis of the observed deviation of filtration and renal blood flow from normal. The kidneys of patients in the nephrotic phase may be enlarged or destruction of parenchymal tissue may be far advanced and contraction inaugurated before the terminal phase is clinically established. If the kidneys are enlarged, reduction in renal blood flow usually encountered implies ischemia of the kidneys. On the other hand, if significant contraction had occurred the figures are compatible with normal perfusion or even hyperemia of tubular tissue. The uniform elevation in the ratio between renal blood flow and Tm_{PAH}, even when the extraction ratio is normal (as in E. H., Table III), gives strong support to the latter possibility. From this it follows that depressed extraction, when present, results from perfusion of inactive tissue rather than arteriovenous shunting. Studies of the hemodynamic effect of concentrated human serum albumin in nephrotics indicate diminished vascular reactivity possibly owing to antecedent vasodilation. On the other hand, certain changes observed in clearances during the course of the disease suggest that renal vasoconstriction may be prominent.

The physiologic effects of concentrated human serum albumin have been subjected to intensive study during recent years. The particulars of the diuretic response and the alterations in circulatory dynamics, body water distribution and renal function are now well known. In common with many other workers[35–38] we have observed augmentations of urine flow, filtration rate and renal blood flow in both normal (six individuals without renal or cardiac disease) and nephrotic (eight patients in the nephrotic phase) subjects. (Table IV.) In our studies relatively small doses of 25 and 50 gm.* have been given slowly and in consequence the effects are not as striking as those of other workers. There was nonetheless a consistent tendency for all these values to increase in almost every case. Of particular interest at this point in the discussion is the fact that the PAH clearance tended to rise. Much more profound changes in this value have been found by other workers. There is no reason to believe that PAH extraction is improved by albumin administration and these values may be taken therefore as good evidence for augmented renal blood flow. Since the blood pressure changes in these acute experiments were small and less than the change in clearances, it may be concluded that arteriolar dilatation occurred. It is interesting that the changes observed in patients with renal disease were smaller than those in the normal subjects and were insignificant in those patients (S. R., S. B., W. H. on September 5, 1947) with the more severe functional disturbance, indicating a reduced renal vascular reactivity as the vasculature is affected progressively by disease. This diminution in reactivity may imply that the renal vascular bed is at or close to its limit of maximal effective cross section or it may indicate irreversible vasoconstriction.

Since nearly all patients in the nephrotic phase progress into the terminal phase, it is to be expected that clearance values and other functions should show a steady decline. In one very cooperative patient (S. H.) we were afforded an unusual opportunity to study spontaneous alterations in function and renal blood flow during the nephrotic phase. The data collected in a study extending over a six-year period are tabulated in Table V.

The patient, a Chinese male of thirty-four years, was admitted to the hospital in December, 1943, two weeks after the sudden onset of generalized edema. He was found to present the typical features of the nephrotic syndrome, nitrogen retention and moderate hematuria

* The serum albumin used in this study was prepared by the American Red Cross from blood of voluntary donors. The conclusions are those of the authors and do not necessarily reflect the policy of the National Blood Program of the American Red Cross.

without any elevation of blood pressure. Shortly after admission renal function studies revealed a marked depression in filtration without an equal disturbance in ERPF. Despite treatment with various diuretic agents and dietary regimens there was no response until two months after admission when diuresis began spontaneously with a weight loss of 15 kg. On discharge in mid-May, 1944, moderate edema persisted and a severe anemia was present, the erythrocyte count having decreased to 2.3 million. He remained in this state throughout the remainder of the year. The renal extraction of PAH was measured in June and used in the correction of clearance values obtained in December because there was no important clinical change during this period. It may be noted that the blood flow relative to Tm_{PAH} (RBF/Tm_{PAH}) was much higher than normal indicating relative hyperemia of functioning tissue despite reduction in PAH clearance, renal blood flow and Tm_{PAH} well below the values obtained at the onset. Four months later these values were more or less the same and the clinical state stationary. During the remainder of 1945 there was noticeable clinical improvement though the nephrotic syndrome persisted and in December, 1945, underwent sudden exacerbation with marked reaccumulation of edema. At this time the protein output ranged between 15 and 20 gm. per day, the PAH clearance and Tm were unchanged from these values three months before, whereas filtration had increased somewhat. Within a few days after the study on December 12, 1945, there was a dramatic reduction in protein loss to between 5 and 10 gm. per day and diuresis began, with significant change in the serum albumin concentration. On December 26, 1945, after weight loss of 10 kg., it was found that the filtration had increased from 58 to 81 cc. per minute in association with an even greater percentile increment in PAH clearance. There was no change in Tm_{PAH}. A few weeks later, after a further weight loss of 2 kg., the filtration rate was still higher (94 cc. per minute) and Tm_{PAH} had increased by 21 per cent. Within the next few months S. H. improved markedly and there has been little recurrence of edema. The serum levels of albumin and cholesterol returned to normal, though the loss of protein in the urine continued. The blood pressure remained within normal limits. In August, 1946, the filtration rate was found to have fallen to a value of 68 cc. per minute and PAH clearance had decreased slightly. Both PAH extraction and Tm_{PAH} were within normal limits at this time. Since this occasion there has been relatively no further clinical change, and renal function studies in 1950 revealed no change in filtration with a further decrease in PAH clearance and a return of Tm to the values obtaining at the onset of the disease.

TABLE V

CHANGES IN RENAL FUNCTION DURING THE COURSE OF THE NEPHROTIC PHASE

(*S. H. Thirty-four year old Chinese Male. S. A.* = $1.53M^2$)

Date	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} %	RBF ml./min.	Tm_{PAH} mg./min.	GFR/Tm_{PAH} ml./mg.	RBF/Tm_{PAH} ml./mg.	Hematocrit	BP mm. Hg
1-18-44	39	568	7	..	...	43	0.90	....	43	120/80
1-29-44	48	558	9	..	...	46	1.04	....	43	122/80
6-29-44	..	...	..	61	...	...	....	....	..	.....
12-11-44	49	324	15	..	(732)*	22	2.23	33.3	28	132/92
4-18-45	50	407	12	76	775	36	1.39	21.5	31	128/84
12-12-45	58	342	17	..	...	31	1.87	....	41	135/90
12-26-45	81	581	14	..	...	38	2.13	....	33	110/75
1-18-46	94	491	19	..	...	46	2.04	....	35	98/70
8-15-46	68	417	16	89	809	64	1.06	12.8	43	108/68
2- 1-50	71	310	23	..	...	47	1.51	...	46	110/70

* This figure is calculated on the basis of E_{PAH} obtained 6/29/44; abbreviations as noted in Tables I and II.

The details of this case are particularly instructive because they reveal how labile inulin or mannitol and PAH clearances may be in the presence of renal disease. It seems reasonable to interpret the sudden change in PAH clearance prior to the onset of

diuresis at the end of 1945 as evidence for sudden vasodilatation since it occurred before any improvement in Tm_{PAH}. Such a phenomenon would seem to indicate that vasoconstriction or some process resembling vasoconstriction in its effect may operate in

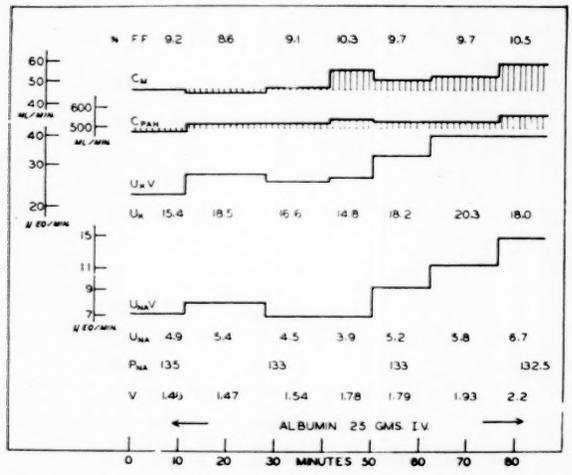

FIG. 3. Effect of salt-poor concentrated human serum albumin on renal function in the nephrotic phase of chronic diffuse glomerulonephritis; the mannitol clearance (C_M—glomerular filtration rate) and PAH clearance (C_{PAH}, here equivalent to renal plasma flow because measured renal PAH extraction remained between 97 and 98 per cent throughout the experiment) were measured before and during slow intravenous administration of 25 gm. of albumin. The patient, E. H., was a twenty-five year old white male in the nephrotic phase of chronic diffuse glomerulonephritis (later proved at necropsy). He had received 50 gm. of salt-poor albumin daily for twelve days immediately prior to this study, and mannitol and PAH clearances had increased from 35 and 260 ml. per minute, respectively, to the values observed during the control period here. The glucose plasma concentration was maintained throughout at about 450 mg. per cent by glucose infusion. With administration of albumin (between arrows) the mannitol clearance increased by as much as 35 per cent and PAH clearance remained more or less constant, so that filtration fraction (FF) increased. With the increment in filtration, urine flow (V) and the urinary output of potassium (U_KV) and sodium ($U_{Na}V$) ions rose. The urinary concentration of sodium (U_{Na}) increased in the absence of change in plasma sodium concentration (P_{Na}). The blood pressure did not change significantly.

the nephrotic phase to reduce blood flow and filtration in the kidney. Edema of the kidney and increased intrarenal tension resulting from loss of water from the blood into the interstitium might also provide the setting for such a process since it has been found[13] that increased intra-abdominal pressure may depress glomerular filtration and renal blood flow. Unfortunately, the factors determining intrarenal pressure are wholly unknown. It is clear that evidence of a characteristic real hemodynamic pattern in the nephrotic phase is lacking. There are indications that both ischemia and hyperemia of functioning parenchymal tissue may occur but whether these result from the operation of local vascular or extravascular mechanisms remain obscure.

The pathogenesis of edema in the nephrotic syndrome, whatever its cause, is a matter of major concern to the clinician since adequate therapy must wait upon clarification of mechanisms. The fact that reduction in oncotic pressure as a result of hypoalbuminemia permits escape of water and solutes from the blood into the tissues is based on adequate evidence.[39] It is obvious that this redistribution may excite renal functional changes that operate to repair the fall in plasma volume and further expand extracellular fluid volume. Accumulation of fluid may be secondary to a change in glomerular filtration or to augmented tubular reabsorption. The evidence favors the latter as the more important though its immediate cause is unknown. The data in Table II disclose no consistent directional change in filtration rate; others[40] have actually found increased filtration in certain cases. Hence, hypofiltration *per se* is an unlikely primary cause for water and salt retention; but studies of albumin-induced or spontaneous diuresis indicate that it may play a subsidiary and at times a predominant role.

The changes observed in filtration following administration of albumin concentrates were small and not directly related in time to the onset of diuresis. However, very small increments in filtration may provide ample filtrate as the basis for diuresis. In view of the crudity of the methods employed it seems not unlikely that such changes might be overlooked or masked by error. Welt and his co-workers[41] believe that albumin produces primarily a water diuresis with subsequent increase in salt excretion as a

result of hypernatremia. In their view increased filtration is not essential or is merely coincidental. The manner in which albumin may excite a water diuresis under these circumstances is obscure. Redistribution of water and electrolytes between the various body compartments occurs and the blood becomes more dilute in terms of the hematocrit but not in terms of other constituents. Hence there is no obvious reason for decrease in the production of antidiuretic hormone by the posterior pituitary. Moreover, natriuresis may occur in the absence of elevated plasma sodium concentration and in clearcut relation to changes in filtration, as in the study of E. H. portrayed in Figure 3. Luetscher and his co-workers[42] have had a similar experience.

The patient, E. H., a twenty-five year old white male, presented himself in the fully developed nephrotic syndrome six weeks after the sudden appearance of edema and heavy proteinuria. Approximately three years prior to admission he suffered an attack of typical acute diffuse glomerulonephritis characterized by marked hematuria and slight facial edema which came on shortly after a severe upper respiratory infection. He recovered uneventfully and remained well until the onset of the nephrotic phase. Concentrated salt-poor human serum albumin was given in daily doses of 50 gm. over a twelve-day period immediately preceding this study. His weight had decreased during the first six days of treatment from 94 to 86 kg. where it remained stationary with persistent gross edema and ascites. Nitrogen balance studies revealed an almost quantitative loss of administered albumin as such in the urine at the end of the period of treatment. Clearance studies revealed an increase in filtration rate and PAH clearances from 35 to 45 ml. per minute and 260 to 504 ml. per minute, respectively, during the period of albumin therapy.* The blood pressure changed from 120/70 to 140/90, hardly enough to account for the alteration in clearances. The serum albumin concentration increased from 0.9 to 1.9 gm. per cent. The blood urea nitrogen fell from 42 to 22, apparently as a result of increased filtration. All these changes were reversed following cessation of therapy. After additional similarly unsuccessful courses of albumin therapy this patient was discharged still suffering from the nephrotic syndrome though edema was reduced. He remained in this stage for a period of one year during which the blood pressure slowly rose to hypertensive levels and renal insufficiency became manifest. At this time edema and the other manifestations of the nephrotic syndrome began to clear and he progressed steadily into uremia. He died a year later and postmortem examination revealed contracted kidneys bearing the typical stigmata of chronic diffuse glomerulonephritis.

The study presented in Figure 3 consisted of measurements of mannitol and PAH clearances, glucose Tm, PAH extraction and sodium and potassium excretion before and during injection of 25 gm. of albumin. It can be seen that the urine flow was low (1.5 ml. per minute) at the beginning despite a plasma glucose level of 450 mg. per cent and heavy glycosuria. Obviously this was an extremely poor response to a powerful osmotic diuretic stimulus. That glucose administration had brought about marked shifts of fluid between the body compartments was evident in a fall in hematocrit from 34 to 27 per cent from the time of starting the glucose infusion to collection of the first urine sample. Slow intravenous administration of 25 gm. of albumin induced definite though small changes in all values without any associated change in hematocrit. The urine flow increased from 1.5 to 2.2 ml. per minute in association with an increase in filtration rate and no significant change in renal blood flow. Both sodium and potassium excretion increased significantly as a result of augmented urinary concentrations and flow in the absence of significant change in plasma levels. It seems evident in this instance that the increment in filtration from 44 to 58 ml. per minute played a determining role since it seems unlikely that the small amount of albumin administered in the setting provided by prolonged preliminary protein treatment and hyperglycemia induced any further profound change in body water distribution or availability. Moreover these effects cannot be ascribed to tubular impairment by filtered protein since

* It should be noted that this response was unusual though it was observed again in E. H. on repetition of the course of treatment. (We are indebted to Dr. Frank Paddock, Pittsfield, Massachusetts, for referring this patient to us.) In four other patients in the nephrotic phase, similar courses of albumin tended rather to depress the clearance values. In all the diuretic response was unsatisfactory and the injected albumin was excreted as such or as nitrogen in the urine.

glucose Tm increased somewhat and PAH extraction remained at 98 per cent.* Finally, the osmotic effect of the filtered protein on the tubular cells must have been much less than that exerted by the glucose escaping reabsorption.

Further evidence that changes in filtration may have a part in promoting diuresis is provided by the observations on S. H. (Table v) in whom a spontaneous diuresis was associated with a significant augmentation of filtration. All these considerations should not obscure the fact that augmented tubular reabsorption of water and electrolyte constitutes the basic cause for fluid retention in the nephrotic phase. This is clearly demonstrable in E. H. (Fig. 3) in whom water and salt excretion were notably reduced despite excess body water and the operation of an osmotic diuretic. It has been shown that the behavior of the nephrotic kidney is qualitatively similar to the behavior of the normal kidney after a period of sodium deprivation[46] but this resemblance does not necessarily imply that the basic causes are similar. There is no reason to believe that sodium in the plasma is not freely available to the nephrotic kidney and the total sodium content of the body may be much greater than normal. It is interesting to speculate upon possible changes in intrarenal tension in this connection. Elevated intra-abdominal pressure induces increased tubular water and sodium reabsorption in the face of water and sodium loading even in the absence of posterior pituitary activity.[47] Elevations in renal venous pressure also have this effect, presumably through the same mechanism.[48] Perhaps edema of the kidney and elevated intrarenal pressure operate in the nephrotic kidney in a similar manner.

It is evident from these comments that patients in the nephrotic phase of glomerulonephritis present remarkable variety. Despite common features of the nephrotic syndrome there is much diversity in renal functional patterns. With few exceptions the renal function deteriorates in time. The determinants of the pace at which this process moves are entirely, and unfortunately, unknown. Some individuals remain in the nephrotic phase or progress into a latent form of the disease marked only by proteinuria over a period of many years (as S. H.). Others progress more rapidly and die in the terminal phase within a period of a few years or even months (as E. H.).

Terminal Phase. The terminal phase of chronic diffuse glomerulonephritis is characterized clinically by uremia and arterial hypertension, pathologically by complete disorganization of renal structure, and physiologically by an amazing variety of derangements. Although life may be prolonged and made comfortable and rewarding for many years in this stage a fatal outcome is inevitable. In the majority of cases the terminal phase appears insidiously without obvious preceding renal disease. The kidney bears only a superficial resemblance to the normal organ and as Oliver[49] points out is no longer a kidney in any strict sense. The number of nephrons is much reduced and those remaining are deformed in various ways. The disappearance of parenchymal tissue has resulted in collapse and irregular shrinkage of the organ with an increase in the relative amount of fibrous tissue. These changes, in addition to active fibroplasia and obstruction by casts, produce further distortion of nephrons. The vasculature is likewise much affected. The blood vessels have become rigid and irregular in distribution. With the obliteration of many glomeruli the arterioles enter directly into the pericapillary network. The vascular system appears to be much reduced in size and complexity. It is not surprising that

* In this and other studies no evidence of interference with tubular function was adduced. The extraction of PAH in one other case remained unchanged during administration of albumin and glucose Tm tended to rise in two others in whom it was measured under similar circumstances. Observations of diminished PAH extraction during albumin administration by Cargill[43] and others[44] were made when much larger doses (75 gm.) were given within the space of a few minutes. Barker et al.[45] suggest that this phenomenon may be a result of large but transient increments in cardiac output and renal blood flow independently of any change in tubular function or intrarenal redistribution of blood.

renal functional changes are extreme and erratic.

Data obtained only in those patients in whom measurements of PAH extraction were made will be considered here and presented in Table VI. Without exception all clearance values were greatly depressed. The mannitol or inulin clearances varied considerably, ranging in this group from 66 to 14 ml. per minute. The gross damage to tubular tissue might permit escape and return of these substances from the tubular lumen to the blood and produce erroneously low values. If simple diffusion from the tubule occurred, one would expect to find discrepancies between the values for inulin and mannitol clearances, since the diffusibility of these substances are so dissimilar. Such discrepancies were not observed here in patients in whom both values were obtained and Earle et al.[24] failed to find lack of agreement between these clearance figures in their studies. Hence, loss by diffusion seems unlikely. It has been suggested[18] that small breaks in the tubule wall would allow tubular fluid to leak into the interstitium and thus into the blood stream but on the basis of the expected hydrostatic differences between these regions one would rather anticipate movement of fluid in the reverse direction which would act to give falsely high figures for filtration. It seems reasonable to accept these clearance values as approximating filtration rate; though large errors are doubtless introduced by such factors as high and possibly variable plasma blanks, the exaggerated effect of incorrect measurements of urine flow and the like. All but three of these individuals presented evidence of nitrogen retention, presumably as a result of lowered filtration. The diminution in filtration can be entirely accounted for by the widespread obliteration of glomeruli rather than by hemodynamic changes.

The PAH clearances were likewise greatly reduced; in some, more and in others, less than filtration. PAH extraction was always depressed and calculations of renal blood flow thus yielded values which were much less changed from normal than the PAH clearances. Nonetheless, the blood flow was decreased, in one patient to less than 200 ml. per minute. Since the arterial pressure was usually elevated, this change in blood flow indicates increased arteriolar resistance; but

TABLE VI

RENAL FUNCTION IN THE TERMINAL PHASE OF CHRONIC DIFFUSE GLOMERULONEPHRITIS*

Subject	S.A.	Sex	Age	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} %	RBF ml./min.	Tm_{PAH} mg./min.	GFR/Tm_{PAH} ml./mg.	RBF/Tm_{PAH} ml./mg.
C. C.	1.62	F	22	60	503	12	81	810	58	1.03	13.9
A. G.	1.66	M	24	62	466	13	99	784	53	1.17	14.8
J. P.	1.84	M	53	66	310	21	90	633	..	....	....
P. W.	1.90	M	17	32	329	10	59	730	20	1.60	36.5
R. W.	2.02	M	26	30	200	15	68	466	25	1.20	18.6
A. B.	2.04	M	24	42	32	+	11	418	Neg.	....	....
T. P.	1.60	M	40	50	149	34	69	293	11	4.54	26.6
S. R.	1.41	M	45	14	22	+	14	240	..	....	....
A. C.	1.66	M	16	19	70	26	56	181	9	2.11	20.1
L. C.†	1.81	F	54	26	32	+	37	113	Neg.	....	....

* Only patients in whom E_{PAH} was determined are included in this table. The diagnosis of chronic diffuse glomerulonephritis in these individuals seemed reasonably certain. The first three (J. P., C. C. and A. G.) were hypertensive but not yet uremic at the time of study. Nitrogen retention developed in all three soon after study and two (J. P. and C. C.) have died. All other patients were in uremia and were hypertensive.

† All have died but necropsy (confirming the diagnosis) was obtained only in L. C. Abbreviations and values are handled as noted in Tables I and II.

+ Filtration fractions were unreasonably high in these individuals in part because PAH concentrations were between 3 and 4 mg. per cent.

increased resistance in this instance must be attributed to the shrinkage in the size of the renal vascular bed as a whole and not to vasoconstriction. Owing to the lack of a reliable method for determining the total and functional masses of the kidney it is difficult to assess renal vasomotor activity in the terminal phase.

Bell[29] has found that the kidneys are contracted to less than half normal weight in more than 60 per cent of patients in azotemia due to chronic diffuse glomerulonephritis. Since a much larger proportion of the weight may be attributed to connective tissue than in the normal, it follows that the parenchyma is usually reduced to an even greater extent. This finding is in harmony with the functional alterations encountered in this and other studies. Maximal tubular PAH transfer (Tm_{PAH}) in four patients in uremia ranged between 9 and 25 mg. per minute and was not measurable in two others (Table VI), indicating a grave disturbance in tubular function probably due both to loss of tubules and to abnormal function of the residue. The last conclusion is supported particularly by inability to measure Tm in two subjects in Table VI and in three others not included there. Indeed, if taken at face value these figures for Tm are negative, suggesting reabsorption or back-diffusion of PAH from the tubules. It is difficult to interpret this as evidence of PAH reabsorption since the causes for error at such low levels of renal function are numerous. Very little or no excretion seems a more likely explanation. There is much additional evidence that residual tubular function is disturbed. Tubular synthesis of ammonia is impaired or altogether lost. Reabsorption of base is defective and sodium and other cations may be lost in dangerously large amounts. As a result of diminished tubular water reabsorption and a loss of concentrating power that eliminates the renal response to antidiuretic hormone of the posterior pituitary, the urine becomes dilute and voluminous in association with disturbances in the pattern of daily urine output. In fact, tubular injury at this stage of the disease seems to exceed the glomerular disorder so that far more filtrate is formed than the defective tubules can handle. As Earle et al.[24] have pointed out this glomerulotubular imbalance may produce a "nephron diuresis" that contributes importantly to the disorders of urine output. The data in Table VI bear out this concept. It can be seen that the GFR/Tm_{PAH} ratio is low or normal in the first three patients in whom it was measured. In two of these uremia had not yet developed. Apparently glomerular and tubular function had decreased in a parallel manner. In the remainder of these subjects, all in profound uremia, a marked disparity between GFR and Tm_{PAH} is evident, denoting more severe impairment of tubular than of glomerular activity at this stage of the disease. In view of these considerations reduction in PAH extraction must be in part a result of impaired tubular removal.

The reduction in renal blood was never as marked as that in Tm_{PAH} so that the RBF/Tm_{PAH} ratio increased. It seems reasonable to interpret this finding as evidence of increased blood flow to the kidney as a whole, as well as to functioning parenchymal tissue in particular. In this view, reduction in PAH extraction results from perfusion of a relatively large mass of functionless scar tissue, to direct communication between arterial and venous channels and perhaps to such excessively rapid perfusion of extractive tubules that there is insufficient time for complete removal. All these considerations support the belief that hyperemia of the kidney is prominent in the terminal phase. Undoubtedly the higher level of arterial pressure accounts in part for this phenomenon but it does not seem essential, since similar values were observed in one individual with a normal blood pressure (S. R.). Vasomotor activity as such appears to be minimal. Administration of albumin to S. R., for example, elicited no change whatever in renal blood flow. However, the problem of renal vascular reactivity in the terminal stage is deserving of more exact and intensive investigation.

The course of events in the terminal

phase is highly erratic. Much depends upon the degree to which disturbances of glomerular and tubular functions permit loss of electrolytes and water. Retention of anions and possibly of various unknown toxic agents may also be important in causing symptomatology. When these derangements are extreme, any conceivable disorder of electrolyte composition and volume of body fluids may arise.[50]

Pyelonephritis

The group of disorders included under this heading have never been adequately characterized. Considerable work during the past twenty-five years arising primarily from the realization that hypertensive disease may be one manifestation of chronic pyelonephritis has been helpful in clarifying certain aspects of the problem. The lack of general agreement regarding incidence, pathogenesis, pathology and course is attributable chiefly to difficulties of diagnosis both in the clinic and the dead-house, to the variety of pathogens and to the vagaries of complicating factors. The renal lesion consists of interstitial infiltrates of leukocytes or tiny abscesses localized principally in the medulla. Because direct invasion of bacteria (E. coli and staphylococci are the major offenders) is concerned, involvement of the kidneys is not at first uniform and therefore may be unilateral or bilateral with one kidney disproportionately affected. Later, as the inflammatory process persists with destruction of renal tissue and cicatricial transformation, both kidneys may change so markedly that the disorder appears diffuse and uniform. The pathologic marks are essentially non-specific at this point and anatomic diagnosis may be impossible. Since symptomatology is minimal and erratic in many individuals, the diagnosis is rarely considered during life. Or when renal dysfunction becomes manifest in association with hypertension, there may be no means of distinguishing the condition from glomerulonephritis or nephrosclerosis, though the nephrotic syndrome apparently rarely or never develops. For these reasons studies of renal function are few and usually limited to patients in the terminal stages of the disease.[51–53]

The localization of the lesions in pyelonephritis close to or about the collecting ducts and the lowermost reaches of the tubule, including the thin segment, might be expected to produce predominantly tubular functional disturbances. Raaschou[53] has measured inulin and diodrast clearances in thirty-two patients with chronic pyelonephritis. The inulin or mannitol clearances were usually reduced, probably more as the result of tubular destruction or obstruction by edema or scar tissue than glomerular obliteration, since many normal glomeruli are found on microscopic examination even when tubular damage is far advanced. Diodrast clearance and Tm were reduced more than filtration, a manifestation Raaschou attributes to the tubular defect. Since depression of the diodrast clearance appeared at more or less the same plasma levels as in normal patients, he believes the tubular damage may be an all-or-nothing phenomenon in which tubule cells either extract diodrast normally or not at all. This also suggests that the process is diffuse rather than focal in its effect. The interesting observation that urea clearance may remain high despite poor urinary concentrating power again points to dissociation of glomerular and tubular injury. The extraction of diodrast in these patients was probably impaired and it may be assumed that renal blood flow was greater than the values for diodrast clearance would indicate. This assumption is supported by data from a study of three patients with chronic pyelonephritis in whom values for PAH extraction were 71, 75 and 86 per cent. (Table VII.) Despite evidence of renal functional impairment the filtration rates were not much reduced in these patients. In agreement with Raaschou's findings the clearance ratios (or filtration fractions) were thus usually increased. The reduction in Tm_{PAH} likewise indicated tubular damage out of proportion to glomerular injury. Renal blood flows were 1,232, 768 and

528 ml. per minute (RBF/Tm_{PAH} ratio—25.3, 58.2 and 10.3, respectively). Three studies alone can not serve as a basis for evaluating relative perfusion but the observed values do suggest that blood flow may be well maintained. Thus, as Raaschou points out, there is physiologic as well as anatomic evidence that tubular damage is preponderant in chronic pyelonephritis. This view finds further support in recent studies of the syndrome of osteomalacia due to renal acidosis.[54–55]

TABLE VII

RENAL FUNCTION IN CHRONIC PYELONEPHRITIS*

Subject	S.A.	Sex	Age	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} %	RBF ml./min.	Tm_{PAH} mg./min.	Tm_g mg./min.	RBF/Tm_{PAH} ml./mg.
C. W.	1.34	F	42	86	315	21	86	528	51	...	10.3
R. B.	1.43	F	15	90	598	15	75	1232	49	...	25.3
E. P.	1.36	F	28	51	396	14	..	....	..	193	....
M. G.	1.56	F	28	62	357	17	71	692	12	125	57.7

* See preceding tables for abbreviations.

Approximately twenty cases of this disturbance have now appeared in the literature. Chronic pyelonephritis has been the underlying renal disease responsible for chronic acidosis in most instances. The predominantly lower nephron injury apparently interferes in these cases with normal excretion of hydrogen ion and synthesis of ammonia, with persistent loss of calcium, sodium and potassium in the urine. Ultimately radiologically detectable bony lesions characterized by bilaterally symmetrical linear infractions (Milkman's syndrome) appear at sites where arteries traverse the bone surface. Albright and his co-workers[54] have found typical histologic alterations of osteomalacia in such areas. Moreover, the biochemical findings (normal serum calcium concentration, reduced serum concentration of phosphate and elevated serum alkaline phosphatase) are typical of osteomalacia. Acidosis in these cases is attributable to a reduction in serum sodium and an elevation in serum chloride concentrations. Three instances of osteomalacia complicating pyelonephritis have been seen at Presbyterian Hospital during the past four years and have been studied in detail by Drs. Pines and Mudge.[55] Ureterolithiasis was prominent in all three; in one following transplantation of the ureters to the colon because of lower urinary tract obstruction and fistula formation, in the second following pyelonephritis in pregnancy and in the third occurring spontaneously. Renal function studies in the last two (E. P. and M. G. —Table VII) revealed maintenance of filtration in the face of impaired tubular function demonstrable in reduced Tm_{PAH}, Tm_D and Tm_G and PAH extraction as in the other patients reported here (R. B. and C. W.—Table VII). The urinary output of potassium was increased in both and in M. G. to such an extent that hypopotassemia, motor weakness and electrocardiographic changes were noted. It is extremely interesting that similar biochemical and osseous changes are seldom observed in chronic diffuse glomerulonephritis. The tubular injury in the terminal phase of glomerulonephritis is as marked as that in pyelonephritis and one might expect to see osteomalacia as frequently. Acidosis, as noted above, is common and hypocalcemia is encountered in association with an osteopathy that may be attributed in part to the effect of chronic acidosis and in part to secondary hyperparathyroidism. In children these changes occur in company with impaired growth and development and radiologic evidence of rickets, though the histologic changes are those of hyperparathyroidism. In glomerulonephritis the filtration rate is usually greatly reduced by the time these changes

take place whereas it is higher or almost normal in pyelonephritis. Since calcium is variously bound to plasma proteins and associated with complex molecular aggregates, its filterability is low. The amount of calcium thus available for filtration is small and the difference in filtration rates between the two conditions may be sufficient to account for a difference in calcium excretion. The sustained filtration in pyelonephritis may thus give rise to heavy loss of calcium and other bases without coincidental retention of phosphate, sulfate or various organic anions. The remarkable response to alkali therapy (all three patients mentioned here have been relieved of symptoms and returned to full activity) suggests that calcium loss is not a product of defective tubular calcium reabsorption but rather a result of facultative excretion of calcium in an effort to maintain acid-base balance.

In its far advanced form there is little to differentiate pyelonephritis from glomerulonephritis on functional grounds. Insufficient evidence is at hand to permit an accurate appraisal of its course. That which is available suggests initial impairment of tubular function with secondary suppression of filtration. Filtration and renal blood flow appear to remain relatively high until late in the disease and may be increased during acute febrile episodes. Hypertension appears under more or less the same circumstances as those in which it appears during chronic glomerulonephritis; viz., when the renal lesion is far advanced, tubular and glomerular function greatly impaired and renal blood flow reduced in absolute terms but increased relative to kidney mass.

THE NEPHROSES

The use of the term "nephrosis" to denote a heterogeneous group of renal diseases characterized by tubular lesions is sanctioned by custom and fixed by habit, although there are serious objections to its retention in medical terminology. In a general way these disorders may be divided into two large groups; one in which proteinuria is prominent and in which the nephrotic syndrome may appear; and another in which tubular necrosis occurs and in which the nephrotic syndrome never develops. The first group bears certain functional resemblances to glomerulonephritis. The principal lesion is glomerular and the clinical or physiologic alterations issue chiefly from this defect. The tubular changes here appear to be the result of excessive protein filtration and/or renal ischemia; inflammation does not seem to play a part. In the group of necrotizing nephroses marked renal arteriolar constriction induced by various stimuli ranging from peripheral circulatory collapse to the direct action of various noxious agents may be an important causative factor. Tubular injury is apparently the result of the direct action of nephrotoxic substances and/or vasoconstrictive ischemia. Many of these disorders are relatively uncommon; others occur acutely and transiently, not providing adequate opportunity or time for careful investigation. As with other workers, our studies of such patients are fragmentary and incomplete. In treating the subject it is necessary to extrapolate tentatively from insufficient data.

Proteinuric Nephroses

So-called benign proteinuria is occasionally encountered in the absence of anamestic data or perceptible evidence of renal disease. In three instances of this kind, all young adults, renal clearances and tubular maxima were within normal limits. Extraction of PAH was measured in one and found normal. Urinary protein loss may be attributable to increased protein filtration but in view of recent work[56] which indicates that a certain proportion of micromolecular protein may be filtered from the plasma in the glomerulus and reabsorbed by the tubules, a defect in tubular protein reabsorption cannot be ruled out.

Orthostatic proteinuria is usually attributed to a change in the permeability of glomerular capillaries resulting from an elevation in renal venous pressure. Renal function

studies in these patients have revealed normal values[57] but recent studies by Bull[58] suggests that filtration and renal blood flow may be reduced in relation to the appearance of proteinuria. This, he believes, is referable to blockage to the outflow of blood from the inferior vena cava by torsion of the liver in the erect position.

Lipoid nephrosis occurs in children as the nephrotic syndrome in the absence of demonstrable renal disease. Increased glomerular capillary permeability appears to be the sole defect. Mannitol or inulin and PAH or diodrast clearances are normal or definitely increased.[40,59] Tubular function does not seem to be impaired. It is generally stated that recovery is the rule and death as a result of renal insufficiency never occurs. This disorder is not encountered in adults. Many workers claim it to be one manifestation of glomerulonephritis. It is certainly true that some patients with typical lipoid nephrosis have progressed into chronic diffuse glomerulonephritis and died in uremia,[60] possibly indicating that the entity "lipoid nephrosis" exists nosologically by definition alone. In this view "lipoid nephrosis" would be considered an acute form of glomerulonephritis from which most children and few or no adults recover completely. More work is necessary to settle this dispute.

Amyloid disease has been considered a disseminated vascular disease because deposits of amyloid often occur in close proximity to capillaries. This is substantially correct with regard to the kidney where amyloid appears in the pericapillary spaces of the glomeruli and to but a small extent elsewhere in the organ.[29] It is now recognized[61] that amyloid deposits are not clearly related to vessels in other tissues. In the kidney this substance decreases capillary permeability in some manner and induces heavy urinary protein loss resulting in the nephrotic syndrome. Few measurements of renal functions have been made. Those available indicate marked impairment of filtration out of proportion to change in PAH clearance.[52] The amyloid deposits finally appear to interfere with blood flow through the glomerulus, destroying it and its attached tubule. In time the amyloid kidney may become scarred and contracted in association with outright renal insufficiency and hypertensive disease. Similar renal functional and anatomic changes may occur in multiple myeloma either as the result of amyloidosis or of damage possibly related to filtration of abnormal globulins.[62]

Intercapillary glomerulosclerosis so resembles amyloidosis anatomically that pathologists have failed to distinguish it until quite recently. Clinically, too, there are many resemblances since with amyloidosis it is one of the few conditions in which uremia, hypertension and the nephrotic syndrome may appear simultaneously. The glomerular lesions (consisting of hyaline nodular masses interposed between the glomerular lobules) may be related to widespread arterial and arteriolar degenerative disease rather than specifically to diabetes mellitus with which it is commonly associated.[29] Shock and his co-workers[63] have found a uniform reduction in all clearances as part of the aging process whereas filtration appears to be particularly affected in diabetic patients.[64] In two individuals with intercapillary glomerulosclerosis observed during this study (both diabetics) mannitol and PAH clearances and Tm_{PAH} were greatly and more or less equally depressed, as others[51,52] have noted.

Necrotizing Nephroses

Attempts to classify this group of nephropathies on the basis of the locus of major damage into upper and lower nephron nephroses are unsatisfactory because the nephron is usually affected as a whole.[65] One or another portion of the nephron may appear to be selectively injured but exceptions are common and isolated involvements rare. In general, two factors seem to be concerned: (1) the direct action of toxic materials upon tubular cells and (2) the effect of vasoconstrictive or obstructive renal ischemia and anoxia.

A large and growing list of compounds is

now known to produce renal injury. Unfortunately many (such as sulfonamides and the heavy metals) are therapeutic agents; others (such as carbon tetrachloride and the other halogenated hydrocarbons) are widely used in industry. Each of these produces tubular necrotizing lesions (often affecting the proximal segment predominantly) that cause oliguria, proteinuria, cylindruria and hematuria, and that may progress to anuria and death in uremia. Providing the dose is small or specific therapeutic agents, such as BAL in heavy metal poisoning, available and quickly used, all these manifestations are quickly reversible. Few studies of renal function have been made because patients are usually so ill that therapy becomes paramount and there is little time for study. Moreover, such studies are difficult or impossible when urine is wanting or obtainable only in very small amounts. Careful studies by Corcoran et al.,[66] Redish et al.[67] and Sirota[68] have revealed marked depressions in all clearance and tubular transfer values shortly after injury by arsenicals, sulfonamide and carbon tetrachloride, respectively. Indeed Tm_{PAH} may be negative. As mentioned earlier, it is possible that these values arise from technical errors unavoidable at such low levels of renal function but both Redish and Sirota prefer to view it here as evidence of escape of filtrate from the tubules. They base this view on Richards'[69] observation of anuria in the presence of visible glomerular filtration in the frog kidney poisoned with mercuric chloride. Anuria or oliguria may be explained in part on this basis and in part by reduction in filtration. Since the diminution in filtration is associated with an equally great reduction in renal blood flow (measured by extraction and clearance technic), intrarenal vasoconstriction and/or augmented intrarenal tissue tension are probably to blame. In experimental animals renal blood flow may be normal early in the course of necrotizing nephroses[70] and it may be surmised that the vasoconstriction observed in man is secondary to the parenchymal insult. There is no evidence of redistribution of blood in the kidney by diversion through juxta-medullary glomeruli since renal arteriovenous oxygen concentration difference remains unchanged. Tubular dysfunction is evident in a reduction in Tm_{PAH} and PAH extraction as well as in the lessened ability to form a concentrated urine, to eliminate acidic ions and to excrete phenol red (PSP). With recovery all values return to normal after a variable period depending upon the extent of injury. Maximal PAH transfer appears to revert within a period of twenty to forty days but PAH clearance and glomerular filtration remain below normal for many more days, suggesting persistence of the factors that interfere with renal blood flow during the acute episode.

Anuria following transfusion of incompatible blood with intravascular hemolysis presents a more difficult problem. In this condition hemoglobin casts fill the distal tubules and collecting ducts, apparently causing obstruction. However, there is increasing evidence that this phenomenon is secondary to diminished filtration following arteriolar constriction. The renal oxygen uptake is normal, indicating absence of arteriovenous shunting. The stimulus to vasoconstriction is obscure. In many cases shock may be implicated but in others this explanation is not satisfactory.

Peripheral circulatory collapse induces marked renal vasoconstriction and hypofiltration in both man and animals.[74,75] If sufficiently protracted irreversible tubular damage occurs. The underlying factors concerned in the pathogenesis of the renal injury following prolonged shock or severe trauma are complex and obscure. First, shock is usually associated with severe tissue damage or crushing injury. It has been shown that destruction of striated muscle may result in the release of large quantities of myohemoglobin which may be nephrotoxic under the conditions imposed by collapse.[76] Burns may similarly release noxious materials and may cause intravascular hemolysis. Secondly, severe shock due to hemorrhage or extreme loss of body water rarely causes irreversible renal damage

but renal ischemia alone may produce tubular necrosis.[77] Hence it is probable that several factors may operate simultaneously to produce the necrotic tubular lesions, characteristically localized in the distal segments. The vasoconstrictive response to shock appears to be diffuse though there is evidence that arterioles in the renal cortex are more seriously involved, and account for the occasional appearance of bilateral cortical necrosis. The fact that PAH extraction may be well sustained during the early phases of experimental shock[75] also indicates continued perfusion of extractive tissue without shunting as suggested by Trueta.[78] It is particularly interesting that renal vasoconstriction may persist for hours or even days after return of arterial pressure and cardiac output to normal. Possibly persistent vasoconstriction of this kind operates to induce permanent damage in some cases despite adequate treatment for collapse.

THE NEPHROSCLEROSES

Essential hypertension is characterized by widespread vasoconstriction which appears to affect the kidney disproportionately.[79] In the usual case this process causes little disturbance of renal function or structure, though local vascular disease is demonstrable. Since there may be moderate scarring and contraction, the renal disorder is often referred to as benign nephrosclerosis. In a few instances the clinical course may undergo striking acceleration in association with the appearance of necrotizing arteriolar lesions which are particularly prominent in the heart, brain and kidneys. Heart failure, hypertensive encephalopathy of varying severity and uremia develop rapidly and soon prove fatal. The renal lesion is devastating and warrants its designation as malignant nephrosclerosis. In some respects this disorder appears to be an independent entity (and indeed it may occur independently of pre-existent hypertensive disease) but it is generally considered a variant of essential hypertension, in part perhaps, because hypertension is always present. Likewise, the hypertensive toxemias of pregnancy present certain distinctive features and may be related to essential hypertension only by coincidence.

Benign Nephrosclerosis

Vascular pathology constitutes the chief renal structural change in benign nephrosclerosis.[20,29] The vascular lesion consists of intimal proliferation in association with sub-intimal hyaline or lipoidal deposits and medial hypertrophy affecting arterioles and small arteries. This process is by no means pathognomonic of hypertensive disease since it occurs in non-hypertensive individuals apparently as a manifestation of aging, increasing in frequency in the older age groups. It appears to be intensified in the course of essential hypertension but the changes are usually not so diffuse that they interfere significantly with perfusion of the kidney. Dilatation (especially of the afferent arterioles) may actually occur. Glomerular involvement is not usually remarkable, obliteration apparently following destruction of the tubule. Atrophic tubules are frequently attached to glomeruli of normal size. On the whole, parenchymal damage is usually lacking (85 per cent of Bell's[29] cases). Clinical manifestations of renal damage are likewise minimal. The chief causes for renal dysfunction in benign nephrosclerosis arise from extrarenal disturbances of prolonged hypertensive disease such as congestive heart failure or coronary occlusion.

Studies of renal function have revealed little evidence of derangement in most instances.[52,80,81] Inulin or mannitol clearances are usually well maintained whereas diodrast or PAH clearances are decreased so that the filtration fraction tends to be high. Since glomerular and tubular involvement tend to advance in parallel, the GFR/Tm_{PAH} ratio shows little consistent change. Other tubular functions are unaffected. The concentrating power remains normal until very late in the disease process and electrolyte and acid excretion are unimpaired. With progression of the disease process all clear-

ance values may decrease markedly but outright renal functional insufficiency is uncommon in the absence of the accelerated phase of hypertensive disease.

The data presented in Table VIII are in agreement with those obtained by other workers. In addition it has been found that PAH extraction is nearly always high or within normal limits. Renal plasma flow and renal blood flow are usually reduced despite the elevation in arterial blood pressure. Since filtration is not equally affected, Smith and his co-workers interpret this change as evidence of efferent arteriolar constriction. Whatever the site of renal vasoconstriction it is evident that benign nephrosclerosis is characterized by ischemia of renal tissue. A smaller decrement in Tm_{PAH} than in renal blood flow with a tendency to low RBF/Tm_{PAH} ratios supports this view. The fact that PAH extraction remains high despite the fall in Tm_{PAH} suggests that blood perfuses only normally functioning tissue and does not flow to abnormal or dying tubules.

There is excellent reason for considering the cause of renal ischemia as functional rather than structural. The renal vasculature has been shown to be normally reactive, responding to pyrogen in a normal fashion by marked vasodilation.[82,83] Such response is illustrated in Figure 4. In this instance pyrogenic inulin produced a fall in arterial pressure (measured directly with the Hamilton manometer) and a rise in cardiac output (measured by the direct Fick method). The renal vasculature participated in the generalized vasodilatation implicit in these changes and renal blood flow (diodrast clearance corrected by the hematocrit) increased. The renal vascular resistance fell to one-half the control values during this study and the tendency for the fraction of cardiac output passing through the kidney to increase suggested more marked vasodilatation in the kidney than in the remainder of the body. Other evidence that the vasoconstrictive process is reversible has emerged from studies of the renal circulation following return of blood pressure to normal after sympathectomy[3] or correction of coarctation of the aorta.[84]

Goldring et al.[80] have found that pyrogenic renal hyperemia may actually increase

TABLE VIII

RENAL FUNCTION IN BENIGN NEPHROSCLEROSIS*

Subject	S.A.	Sex	Age	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} %	RBF ml./min.	Tm_{PAH} mg./min.	GFR/Tm_{PAH} ml./mg.	RBF/Tm_{PAH} ml./mg.
H. G.	1.55	F	33	135	645	21	98	1335	....	....	....
N. P.	1.75	M	53	154	643	24	90	1310	103	1.49	12.6
L. S.	1.65	F	21	104	555	19	100	999	73	1.42	13.6
G. S.	1.98	M	42	127	534	24	90	986	81	1.57	12.2
H. S.	1.68	M	35	80	419	19	92	954	...	....	....
J. D.	1.88	M	38	53	523	10	93	953	...	....	....
J. P.	1.38	F	18	121	444	26	90	912	66	1.82	13.8
J. W.	1.72	M	48	77	379	20	82	906	...	....	....
E. P.	1.72	F	52	122	525	23	90	888	97	1.27	9.2
E. T.	1.60	F	17	85	409	21	87	862	...	....	....
W. H.	1.63	F	64	74	444	17	88	740	65	1.14	11.4
C. C.	1.79	M	44	97	405	24	92	728	69	1.40	10.6
M. St. J.	1.55	M	49	115	396	29	86	685	56	2.06	12.3
M. H.	1.81	F	54	118	390	30	96	637	90	1.31	7.5
M. McK.	1.41	F	55	94	355	27	93	633	53	1.79	12.0

* Only patients in whom E_{PAH} was determined are included in this table and arranged in order of RBF. Every individual suffered from essential hypertension of several years duration. There was no evidence of cardiac insufficiency. In nearly every patient moderate proteinuria was observed from time to time; abbreviations and values handled as in Tables I and II.

diodrast Tm from 10 to 33 per cent apparently "demonstrating that substantial portions of renal parenchyma capable of excreting diodrast were not available to perfusion under basal conditions."[3] This observation appears to imply the presence

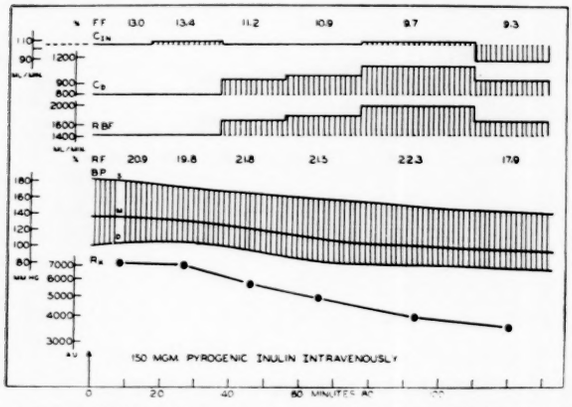

FIG. 4. Effect of pyrogenic reaction on renal function in essential hypertension; toxic inulin of known pyrogenicity was administered intravenously to H. H., a forty-nine year old white male with well established essential hypertension at time noted in figure by arrow. Inulin clearance (C_{in}—glomerular filtration rate) diodrast clearance (C_D—renal plasma flow) and filtration fraction (FF—C_{in}/C_D) were measured simultaneously with determinations of femoral arterial pressure (BP—Hamilton manometer) and cardiac output (direct Fick). Values for systolic (S), diastolic (D) and mean (M) pressures are charted here. Renal blood flow (RBF) was calculated from the diodrast clearance and the hematocrit. Following administration of the pyrogen, C_D and RBF increased without change in glomerular filtration. The blood pressure fell steadily throughout despite increase in cardiac output (not shown here), indicating diminished peripheral vascular resistance. The renal vascular resistance (R_k) calculated from the values for RBF and mean arterial pressure and expressed in absolute units (dynes cm^{-5} sec.) fell sharply. Since the fraction of cardiac output passing through the kidney (renal fraction, calculated from RBF and the cardiac output) tended to rise, vasodilation was probably more marked in the kidney than elsewhere. The body temperature remained normal throughout the study because the patient had been pre-medicated with aminopyrine.

of focal ischemia in some areas. Nonetheless, the vasoconstrictive process is surprisingly diffuse. Chasis and Redish[85] have shown that both kidneys are uniformly affected. Moreover, there is a good correlation between glucose tubular loading and tubular reabsorption so that all tubules appear to be saturated at about the same plasma concentration of glucose as in the normal.[86] This finding is consistent with uniform depression of glomerular perfusion.

Malignant Nephrosclerosis

Necrotizing arteriolitis, intense and widespread subintimal hyalinization and collagenous intimal thickening of renal arterioles appears characteristically in malignant nephrosclerosis.[29,87] The necrotic lesions of the arteriolar walls are often associated with thrombosis. Atrophy of the tubules varies greatly, apparently depending upon the duration of the vascular disease.

The data presented in Table IX indicate that filtration may range from 66 to 13 ml. per minute. This low filtration is in keeping with the observed nitrogen retention and other evidences of renal insufficiency observed in all these patients and it is consistent with the known anatomic alterations. On the whole, however, the values for filtration were somewhat higher than one might have expected on the basis of the change observed in Tm_{PAH}. This value tended to fall more than filtration so that the GFR/Tm_{PAH} ratio rose above normal, suggesting increased filtration pressure possibly arising from the striking elevation in arterial pressure and/or afferent arteriolar vasodilatation. The change was probably even more marked since failure to correct calculated Tm_{PAH} for the hypoproteinemia observed in these patients probably resulted in overestimation of Tm_{PAH}.

The PAH clearance was nearly always greatly diminished both as a result of reduced renal blood flow and lessened PAH extraction. The change in extraction may indicate perfusion of non-functioning tissue as well as inability of the still operating units to remove PAH from the blood. The maintenance of blood flow relative to Tm_{PAH} was somewhat surprising, however, since RBF/Tm_{PAH} ratio actually rose well above normal in four of seven subjects and in view of the possible error in Tm_{PAH} may have been high in the remainder. In this respect the renal circulatory derangement in malignant nephrosclerosis resembles that of chronic diffuse glomerulonephritis, pos-

sibly indicating here, too, relative hyperemia of the kidney. The fact that patients in what appears to be the same stage of the disease also fail to respond to pyrogen with vasodilatation might be explained as a result of prior development of maximal

may be very large relative to the mass of functioning tubular tissue detectable by functional studies suggests hyperemia not ischemia. Smith[19] has suggested that tubular atrophy might result in functionless "impotent" tubules in which filtration continues

TABLE IX

RENAL FUNCTION IN MALIGNANT NEPHROSCLEROSIS*

Subject	S.A.	Sex	Age	GFR ml./min.	ERPF ml./min.	F.F. %	E_{PAH} %	RBF ml./min.	Tm_{PAH} mg./min.	GFR/Tm_{PAH} ml./mg.	RBF/Tm_{PAH} ml./mg.
M. G.	1.73	M	40	46	248	19	61	683	23	2.00	29.6
L. H.	1.87	M	37	66	228	29	85	532	45	1.47	11.8
E. McE.	1.37	F	54	26	99	27	31	496	14	1.86	35.7
J. W.	1.60	M	39	20	97	21	33	419	..	....	....
J. R.	1.70	M	45	33	133	24	72	334	23	1.44	14.5
E. McT.	1.60	M	54	34	134	25	77	326	24	1.42	13.6
A. M.	1.53	F	43	66	185	36	85	323	30	2.20	11.0
G. S.	1.60	M	27	13	71	19	37	308	8	1.63	38.5
H. B.	1.56	F	43	33	118	28	68	284	..	....	....
M. W.	1.68	F	47	48	116	42	68	232	11	4.36	21.1

* Only patients in whom E_{PAH} was determined are included in this table and arranged in order of RBF. With the exception of L. H. all were in uremia associated with papilledema, marked hypertension and evidence of diminished cardiac reserve. L. H. suffered previously from severe heart failure in the course of rapidly advancing hypertensive disease, dying shortly after this study as a result of a cerebrovascular accident. All but J. R. and H. B. have died, autopsy confirming the diagnosis was obtainable only in G. S.; abbreviations and values handled as in Tables I and II.

dilatation. Certainly vascular reactivity is diminished or absent.

The syndrome of malignant nephrosclerosis is difficult to appraise in functional terms. Its development in the course of essential hypertension, its inevitable association with elevated blood pressure, and its renal pathology strongly suggest that it is the end stage of the hypertensive process accelerated by factors as yet unknown. Arteriolitis thus could be considered a manifestation and possibly a result of a strongly vasoconstrictive process that is responsible for the rise in pressure, cerebrovascular disturbances and destruction of renal tissue. Or possibly, a separate vascular disorder, to which hypertensive patients are particularly susceptible, manifests itself in this manner. In either case a vasoconstrictive ischemia of the kidney is postulated as the cause of tubular atrophy. Such a mechanism would be reasonable in view of the renal functional and vascular changes noted in benign nephrosclerosis. But the observation that renal blood flow in malignant nephrosclerosis thus accounting for high GFR/Tm_{PAH} and RBF/Tm_{PAH} ratios. It is difficult to understand how such tubules are affected by ischemia if blood continues to perfuse their glomeruli and if interstitial fluid circulation is of any moment. Here, as in glomerulonephritis, interference with blood flow appears to follow parenchymal damage. In glomerulonephritis this is a reasonable sequence because filtration is disturbed early and tubules apparently become atrophic and finally die when they no longer serve any useful purpose in processing filtrate. In malignant nephrosclerosis, filtration continues to be good relative to tubular function and the cause of tubular dysfunction must be sought for elsewhere. It is interesting to speculate on the possibility that malignant nephrosclerosis may be as much a disorder of renal tubular cells as of the renal vasculature.

Hypertensive Toxemia of Pregnancy

The clinical hall-marks of hypertensive toxemia of pregnancy are elevation of

arterial pressure above the prepartum level, proteinuria and edema at some time in the last five months of pregnancy. Azotemia and hematuria are rare, except in very severe cases. Characteristically, all these disturbances clear quickly following delivery. In about one-fourth, hypertension, proteinuria or both may persist. These manifestations are similar to those encountered in acute diffuse glomerulonephritis and they are associated with diffuse glomerular lesions consisting of thickened basement membrane and endothelial proliferation. As in acute nephritis the glomeruli may be almost bloodless. Fatty and hyaline droplets are found in the tubular cells. Lesions resembling those of nephrosclerosis or chronic diffuse glomerulonephritis are encountered in patients dying in the course of post-toxemic vascular disease.[88]

Renal function is not seriously impaired in the majority of cases during the acute toxemic episode. Although the serum uric acid concentration may rise, the blood urea nitrogen level is usually within normal limits. Glomerular filtration appears to be reduced somewhat whereas effective renal blood flow remains unchanged or rises.[89] This functional pattern resembles that of acute nephritis. With recovery following delivery the clearance values return to normal or, if hypertension persists, show the changes observed in benign nephrosclerosis.

The position of this disorder relative to glomerulonephritis and nephrosclerosis remains obscure. The evidence that it may initiate hypertensive disease is unsatisfactory owing to insufficient information regarding the prepartum state. On the basis of the data now available hypertensive toxemia could be considered with equal validity a manifestation of glomerulonephritis.

CONGENITAL DISORDERS OF THE KIDNEY

Congenital disorders of the kidney may be conveniently divided into two groups: (1) those in which structural malformation has occurred and (2) those in which there is an abnormality of cellular function, probably biochemical in nature. These changes are not necessarily hereditary nor are they wholly limited to early life. Analogous alterations in structure or function could conceivably develop late in life as secondary manifestations of renal disease; or defects present at birth may not become evident clinically until progression or some secondary disease process unmasks them. Severe structural deformities of the kidney such as agenesis or hypoplasia may be completely incompatible with life or provide such a suitable setting for infection and pyelonephritis that functional studies of the primary condition have been unobtainable. On the other hand, ectopia and fusion of the kidneys appear to cause little change in function provided urinary drainage is normal though exact studies have never been made.

Polycystic disease of the kidney has been shown to be present at birth. Its cause remains unknown. In certain cases malunion of the anlagen of glomeruli and tubules probably occurs with the formation of numerous tiny cystic structures that grow larger as the years pass, gradually increasing the total size of the kidneys and by their crowding ultimately destroying most of the functional parenchyma. This failure of union may be so widespread that kidney function is never normal and death occurs in uremia at an early age. Often, however, the condition is symptomless and remains undiscovered throughout life or until after the fourth or fifth decade. In these it is possible that crops of primitive nephrons, ontogenetic predecessors of the mature structures, fail to disappear by atrophy as in the normal and remain as cysts. Recent studies by Lambert[90] and others have shown that the cystic structures may also arise from dysplastic alteration of the tubule walls. In these areas the tubule wall balloons out and becomes cystic. Many cysts eventually part company with their parent tubules and grow slowly as isolated structures. Others remain as part of the tubule. Lambert has injected inulin intravenously in two patients with polycystic disease shortly before death and found inulin present in the cystic fluid

in higher concentration than in the blood, indicating continued filtration by the glomeruli and water reabsorption by the tubule of which the cyst is a part. Unfortunately, measurements of filtration and blood flow are not available early in the disease process. It seems likely, however, that this observation provides a partial explanation for the puzzling clinical impression that such patients tend to do fairly well for years despite marked azotemia.

Congenital metabolic disorders of renal tubule cells are much more difficult to define than anatomic defects. It would seem reasonable to expect isolated disturbances of tubular reabsorption of water, electrolytes, glucose, amino acids and other substances, but the intracellular systems involved are exceedingly complex, closely related to essential processes in all body cells and dependent in part upon extrarenal influences. Thus pituitary and adrenal diseases are known to produce more or less isolated defects in tubular water and sodium reabsorption, respectively, that are speedily reversible by appropriate substitution therapy. Similar manifestations could be produced by disturbances at the tubular level. Renal glycosuria is generally acknowledged as a failure of tubular glucose reabsorption but other conditions of the same kind are more obscure.

Renal glycosuria is clearly inherited in many instances, often detected in early childhood and persists throughout life without ill effect. In others it apparently develops later in life. The failure of the tubules to reabsorb glucose completely from the glomerular filtrate cannot be ascribed to widespread renal disease since all studies concur in showing normal kidney function in all other aspects. Friedman and his co-workers[91] have reported studies of five patients which indicate that maximal glucose reabsorption (Tm_g) is within normal limits whereas Govaerts and Lambert[92] and Nielson[93] have each reported an instance in which the value for Tm_g was greatly depressed. Reduction in maximal glucose reabsorption capacity might be sufficient to give rise to glycosuria at normal concentrations of glucose in the blood, provided filtration rate remains high. Thus glycosuria is uncommon in chronic renal disease despite marked diminution of Tm_g because filtration falls to about the same extent. In the individual with renal glycosuria, however, filtration is normal. Hence at the usual plasma levels enough glucose may be filtered to saturate the tubular reabsorptive mechanisms. The cause for a decrease in Tm_g in the absence of changes in other renal functions is not clear. A discrete lesion of the transfer system, perhaps involving a single enzyme, has been suggested. It is somewhat more difficult to account for glycosuria when Tm_g is normal or almost so. The evidence that maximal glucose reabsorption may be normal in some cases seems wholly acceptable. Studies in this laboratory have disclosed almost normal values in three of five patients with proved renal glycosuria. (Fig. 5.) A family history of the disorder was obtained in two of these (C. L.* and D. A.), and in the third (H. P.) the defect was first detected at the age of fourteen, two years prior to study. Friedman and others[94] have pointed out the fact that glycosuria occurs at much lower tubular glucose loads than in the normal. This was also demonstrable in two of these three cases (Fig. 5) during gradual elevation of the blood level of glucose from low to high levels. Normally there is complete tubular reabsorption of glucose up to the level at which saturation occurs. Thus the rate of reabsorption (T) at low glucose concentrations is equal to the rate of glucose filtration, i.e., the glucose load, calculated from the filtration rate and the plasma glucose concentration. These values (T and Load) may be expressed as ratios in terms of Tm_g in order to obtain strictly comparable curves in different individuals. As shown in the figure, the load/Tm_g ratio and T/Tm_g ratio are theoretically equal until Tm is reached when the T/Tm ratio remains at

* We are indebted to Dr. Howard Root, New England Deaconess Hospital, Boston, for referring this patient to us for study.

unity regardless of further changes in load. And in practice the figures normally follow the straight lines (titration curve) in Figure 5 quite well. In these two patients with renal glycosuria there is a definite deviation from the theoretic at all loads. This splay in the

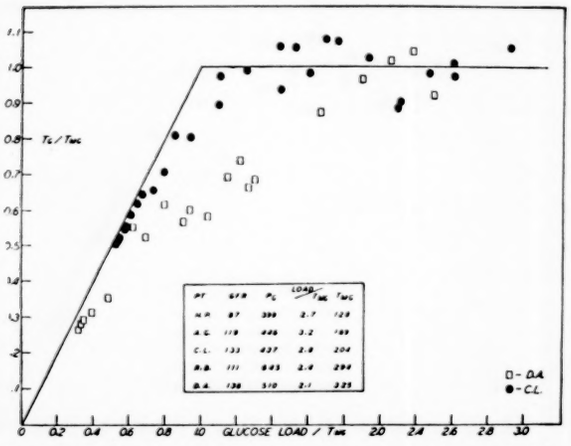

FIG. 5. Tubular reabsorption of glucose in renal diabetes. Values (corrected to a body surface of 1.73 M^2) for glomerular filtration rate (GFR) and maximal tubular glucose reabsorption (Tm_g) in five patients (Pt) with proved renal diabetes are presented in the table. In three (C. L., R. B. and D. A.) the diagnosis was made in childhood; in two (H. P. and A. G.) the disorder was discovered later in life. Both C. L. and D. A. had a clear-cut family history of this abnormality. The values for filtration were within normal limits in all except H. P. who was found also to have an abnormally low Tm_g. Maximal glucose reabsorption was reduced below mean normal in all, but was not greatly diminished in R. B. and D. A. Successful measurements of glucose reabsorption during continuous elevation of the plasma glucose level were possible only in D. A. and C. L., and are presented here in relation to the theoretic "titration curve" (straight lines). The values for glucose reabsorption (T_g—expressed here in terms of the average value of Tm_g as the Tg/Tm_g ratio) are plotted against figures for glucose load (calculated from the observed glucose plasma level and the average filtration rate determined simultaneously and expressed here in terms of Tm_g as the $Load/Tm_g$ ratio). It may be seen that the values for reabsorption (open squares, D. A.; closed circles, C. L.) fell below the theoretic curve at all levels of loading. This splay was most marked in D. A.

titration curve may be explained in various ways. It has been suggested that the phenomenon might result from interference with movement of glucose across the cellular membrane or to a change in the rate at which glucose enters into the transfer system. Another explanation may be based upon anatomic grounds. The close agreement between observed and theoretic titration curves in the normal suggests a nice functional balance between each glomerulus and its attached tubule, remarkable uniformity of the nephron population or both. Introduction of even a small anatomic variation or a decrete and localized tubular defect would upset this balance without significantly affecting over-all clearance values. Thus a rearrangement of glomeruli and tubules in such a manner that large glomeruli are attached to small tubules and small tubules to large glomeruli might produce splayed curves. A discrete anatomic tubular anomaly without corresponding glomerular change affecting 10 per cent of the nephrons would not be readily detectable by anatomic methods but would permit heavy glycosuria at the usual plasma glucose concentrations. It is impossible at present to say with any certainty whether the defect is a general disturbance in which all glucose reabsorbing cells are involved or one in which a discrete and well localized lesion has occurred. In the remaining two subjects (A. G. and H. P.) glycosuria could be attributed to low values for Tm_g in association with such high values for filtration that the load of glucose at the normal plasma glucose concentrations approached the saturation limit. Since glycosuria in these two cases apparently developed in adulthood it is possible that the tubular disorder was secondary to renal disease of some kind. The evidence available suggests that two varieties of the disorder may be encountered; one characterized by normal or nearly normal Tm_g and by a familial tendency, possibly in association with congenital anomaly of the renal tubules; the other, by low values for Tm_g in older individuals, possibly due to a generalized disturbance.

Aminoaciduria, like glycosuria, may arise from an apparently limited tubular dysfunction. This anomaly is occasionally encountered in children in company with renal glycosuria and hyperphosphaturia (Fanconi syndrome) presumably indicating

a developmental defect of the tubules that interferes with normal reabsorption of glucose and phosphate as well as amino acids. Despite adequate mechanisms for acidification of the urine and synthesis of ammonia, the excretion of acid is so large that efficient base-sparing activity is impossible and a chronic acidosis ensues. In addition, hypophosphatemia with or without hypocalcemia may develop. Rachitic dwarfism or osteomalacia occur as a consequence of these biochemical changes.[95,96] Very few of these individuals have been studied with care and insufficient data are available to provide a clear picture of the fundamental renal functional alterations. There is evidence that filtration and renal blood flow may be relatively undisturbed even when the tubular lesion is severe.[95] However, demonstrable nephrocalcinosis and postmortem studies as well as the occasional appearance of azotemia indicate that glomerular damage and tubular destruction may occur. It is interesting that cystinosis with cystine deposits and cystine calculi in the kidney and hepatic cirrhosis are encountered in many instances of Fanconi's syndrome. Recent studies have disclosed a consistent marked elevation in urinary excretion of amino acids in Wilson's disease or hepatolenticular degeneration.[97,98] This disturbance appears to arise from defective tubular reabsorption of amino acids. In a few cases renal glycosuria has been observed.[98] Bony lesions are rarely if ever present. These facts suggest an interrelationship between a number of rather obscure disorders affecting the liver, kidney and amino acid metabolism. Further work is necessary to define the role of the tubular lesion in the pathogenesis of these conditions. It is not unlikely that similar dysfunctions may arise in the course of such diseases as glomerulonephritis or pyelonephritis when tubular damage is excessive or preponderant.

Williams and Henry[99] have suggested that diabetes insipidus may sometimes occur as a result of a congenital tubular lesion. They studied one member of a family in which pitressin-resistant diabetes insipidus occurred sporadically over five generations in seven individuals, all males, apparently as the result of the transmission of a six-linked character through females. Renal function studies revealed normal filtration and normal maximal glucose reabsorptive capacity. Both diodrast clearance and diodrast Tm were significantly reduced. Since their patient reacted normally to pitressin in all other respects and since his serum and body cells did not inactivate pitression more rapidly than the normal, they believe that failure to reabsorb water reflected a specific renal tubular defect which also interfered with diodrast excretion.

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REFERENCES

1. Bradley, S. E., Curry, J. J. and Bradley, G. P. Renal extraction of p-aminohippurate in normal subjects and in essential hypertension and chronic diffuse glomerulonephritis. *Federation Proc.*, 6: 79–80, 1947.
2. Bradley, S. E. The validity of the clearance technique in the measurement of renal blood flow in normal man and in patients with essential hypertension. Tr. Josiah Macy Jr. Foundation Conference on Factors Regulating Blood Pressure, 1: 118–123, 1947.
3. Goldring, W. and Chasis, H. Hypertension and Hypertensive Disease. New York, 1944. The Commonwealth Fund.
4. Fujita, A. and Iwatake, D. Bestimmung des echten Blutzuckers ohne Hefe. *Biochem. Ztschr.*, 242: 43–60, 1941.
5. Smith, H. W., Finkelstein, N., Aliminosa, L., Crawford, B. and Graber, M. The renal clearances of substituted hippuric acid derivatives and other aromatic acids in dog and man. *J. Clin. Investigation*, 24: 388–404, 1945.
6. Harrison, H. E. A modification of the diphenylamine method for determination of inulin. *Proc. Soc. Exper. Biol. & Med.*, 49: 111–114, 1942.
7. Smith, W. W., Finkelstein, N. and Smith, H. W. Renal excretion of hexitols (sorbitol, mannitol, and dulcitol) and their derivatives (sorbitan, isomannide, and sorbide) and of endogenous creatinine-like chromogen in dog and man. *J. Biol. Chem.*, 135: 231–250, 1940.
8. Barker, H. G. and Clark, J. K. Effect of para-aminohippurate on mannitol determinations by

the periodate-iodide-thiosulfate method. *Proc. Soc. Exper. Biol. & Med.*, 64: 120–122, 1947.

9. Alpert, L. K. A rapid method for the determination of diodrast-iodine in blood and urine. *Bull. Johns Hopkins Hosp.*, 68: 522–537, 1941.
10. Nelson, N. A photometric adaptation of the Somogyi method for the determination of glucose. *J. Biol. Chem.*, 153: 375–380, 1944.
11. Josephson, B., Werkö, L. and Bucht, H. The renal extraction of diodrast in man. *Scandinav. J. Clin. & Lab. Investigation*, 2: 149–151, 1950.
12. White, H. L. Observations on the behavior of diodrast in the dog. *Am. J. Physiol.*, 130: 454–463, 1940.
13. Bradley, S. E. and Bradley, G. P. The effect of increased intra-abdominal pressure on renal function in man. *J. Clin. Investigation*, 26: 1010–1022, 1947.
14. Schmidt, C. F. and Hayman, J. M., Jr. A note on lymph formation in the dog's kidney and the effect of certain diuretics upon it. *Am. J. Physiol.*, 91: 151–160, 1929.
15. Berger, E. Y., Farber, S. J. and Earle, D. P., Jr. Renal excretion of mannitol. *Proc. Soc. Exper. Biol. & Med.*, 66: 62–66, 1947.
16. Brandt, J. L. and Baker, K. A study of methods for determining the glomerular filtration rate in man and animals by the use of inulin, mannitol, and creatinine; with a presentation of a method for measuring the inulin clearance. In preparation.
17. Bobey, M. E., Longley, L. P., Dickes, R., Price, J. W. and Hayman, J. M., Jr. Effect of uranium poisoning on plasma diodrast clearance and renal plasma flow in the dog. *Am. J. Physiol.*, 139: 155–160, 1943.
18. Oliver, J., Bloom, F. and MacDowell, M. Structural and functional transformations in the tubular epithelium of the dog's kidney in chronic Bright's disease and their relation to mechanisms of renal compensation and failure. *J. Exper. Med.*, 73: 141–160, 1941.
19. Smith, H. W. Note on the interpretation of clearance methods in the diseased kidney. *J. Clin. Investigation*, 20: 631–635, 1941.
20. Oliver, J. Architecture of the Kidney in Chronic Bright's Disease. New York, 1939. Paul B. Hoeber, Inc.
21. Bradley, S. E. and Bradley, G. P. Renal function during chronic anemia in man. *Blood*, 2: 192–202, 1947.
22. Chasis, H., Ranges, H. A., Goldring, W. and Smith, H. W. The control of renal blood flow and glomerular filtration in normal man. *J. Clin. Investigation*, 17: 683–697, 1938.
23. Scott, H. W., Jr. and Elliott, S. R., ii. Renal hemodynamics in congenital cyanotic heart disease. *Bull. Johns Hopkins Hosp.*, 86: 58–71, 1950.
24. Earle, D. P., Jr., Taggart, J. V. and Shannon, J. A. Glomerulonephritis. A survey of the functional organization of the kidney in various stages of diffuse glomerulonephritis. *J. Clin. Investigation*, 23: 119–137, 1944.
25. Findley, T., Edwards, J. C., Clinton, E. and White, H. L. Clearance of diodrast, phenolsulphonephthalein and inulin in hypertension and in nephritis. *Arch. Int. Med.*, 70: 935–947, 1942.
26. Black, D. A. K., Platt, R., Rowlands, E. N. and Varley, H. Renal hemodynamics in acute nephritis. *Clin. Sc.*, 6: 295–302, 1948.
27. Hilden, T. Diodrast clearance in acute nephritis. *Acta med. Scandinav.*, 106: 1–7, 1943.
28. Cargill, W. H. The measurement of glomerular and tubular plasma flow in the normal and diseased human kidney. *J. Clin. Investigation*, 28: 533–538, 1949.
29. Bell, E. T. Renal Diseases. Philadelphia, 1946. Lea & Febiger.
30. Smith, H. W. Lectures on the Kidney. Lawrence, Kan., 1943. University Extension Division, University of Kansas.
31. Selkurt, E. E., Hall, P. W., and Spencer, M. P. Graded arterial pressure decrement and renal clearance of PAH, creatinine and sodium. *Federation Proc.*, 8: 143, 1949.
32. Pitts, R. F. and Duggan, J. J. Studies on diuretics. ii. The relationship between glomerular filtration rate, proximal tubular absorption of sodium and diuretic efficacy of mercurials. *J. Clin. Investigation*, 29: 372–379, 1950.
33. Cargill, W. H. and Hickam, J. B. The oxygen consumption of the normal and the diseased human kidney. *J. Clin. Investigation*, 28: 526–532, 1949.
34. Ellis, A. Natural history of Bright's disease: clinical, histological and experimental observations. *Lancet*, 1: 1–7, 34–36, 72–76, 1942.
35. Patek, A. J., Jr., Mankin, H., Colcher, H., Lowell, A. and Earle, D. P., Jr. The effects of intravenous injection of concentrated human serum albumin upon blood plasma, ascites and renal functions in three patients with cirrhosis of the liver. *J. Clin. Investigation*, 27: 135–144, 1948.
36. Eder, H. A., Chinard, F. P., Greif, R. L., Cotzias, G. C., Hiller, A., Van Slyke, D. D. and Lauson, H. D. A study of the changes in plasma volume, renal function, and water and salt balance induced by repeated administration of human plasma albumin to patients with the nephrotic syndrome. *J. Clin. Investigation*, 27: 532, 1948.
37. Cargill, W. H. Effect of the intravenous administration of human serum albumin on renal function. *Proc. Soc. Exper. Biol. & Med.*, 68: 189–192, 1948.
38. Goodyear, A. V. N., Peterson, E. R. and Relman, A. S. Some effects of albumin infusions on renal function and electrolyte excretion in normal man. *J. Appl. Physiol.*, 1: 671–682, 1949.
39. Bradley, S. E. and Tyson, C. J. The "nephrotic syndrome." *New England J. Med.*, 238: 223–227, 260–266, 1948.
40. Emerson, K., Jr. and Dole, V. P. Diodrast and inulin clearances in nephrotic children with supernormal urea clearances. *J. Clin. Investigation*, 22: 447–450, 1943.
41. Orloff, J., Welt, L. G. and Stowe, L. The effects of concentrated salt-poor albumin on the metabolism and excretion of water and electrolytes in

nephrosis and toxemia of pregnancy. *J. Clin. Investigation*, 29: 770–780, 1950.

42. Luetscher, J. A., Jr., Hall, A. D. and Kremer, V. L. Treatment of nephrosis with concentrated human serum albumin. II. Effects on renal function and on excretion of water and some electrolytes. *J. Clin. Investigation*, 29: 896–904, 1950.
43. Cargill, W. H. Effect of human serum albumin on renal hemodynamics and the tubular extraction of para-amino hippuric acid. *Am. J. Med.*, 4: 461–462, 1948.
44. Mitchie, A. J., Gimbel, N. S. and Riegel, C. Renal hemodynamics during short and long periods of salt poor albumin administration. *Federation Proc.*, 8: 110, 1949.
45. Barker, H. G., Clark, J. K., Croley, A. P. and Cummins, A. J. Effect of albumin on renal oxygen consumption in man. *Federation Proc.*, 9: 8, 1950.
46. Loeb, R. F., Atchley, D. W., Richards, D. W., Jr., Benedict, E. M. and Driscoll, M. E. On the mechanism of nephrotic edema. *J. Clin. Investigation*, 11: 621–639, 1932.
47. Bradley, S. E., Mudge, G. H., Blake, W. D. and Alphonse, P. The effect of increased intra-abdominal pressure upon renal excretion of water, sodium and potassium in normal human subjects and in patients with diabetes insipidus. *J. Clin. Investigation*, 28: 772, 1949.
48. Blake, W. D., Wègria, R., Keating, R. P. and Ward, H. P. Effect of increased renal venous pressure on renal function. *Am. J. Physiol.*, 157: 1–13, 1949.
49. Oliver, J. When is the kidney not a kidney? *J. Urol.*, 63: 373–402, 1950.
50. Bradley, S. E. The Pathologic Physiology of Uremia in Chronic Bright's Disease. Springfield, Ill., 1948. Charles C Thomas.
51. Corcoran, A. C., Taylor, R. D. and Page, I. H. Functional patterns in renal disease. *Ann. Int. Med.*, 28: 560–582, 1948.
52. Earle, D. P., Jr. Renal function tests in the diagnosis of glomerular and tubular disease. *Bull. New York Acad. Med.*, 26: 47–65, 1950.
53. Raaschou, F. Studies of Chronic Pyelonephritis with Special Reference to the Kidney Function. Copenhagen, 1948. Ejnar Munkgaard.
54. Albright, F., Burnett, C. H., Parson, W., Reifenstein, E. C., Jr. and Roos, A. Osteomalacia and late rickets. *Medicine*, 25: 399–479, 1946.
55. Pines, K. L. and Mudge, G. H. Renal tubular acidosis with osteomalacia: report of three cases. In preparation.
56. Terry, R., Hawkins, D. R., Church, E. H. and Whipple, G. H. Proteinuria related to hyperproteinemia in dogs following plasma given parenterally. *J. Exper. Med.*, 87: 561–573, 1948.
57. Rytand, D. Roentgenographic study of orthostatic albuminuria by means of injections of diodrast. *Arch. Int. Med.*, 59: 837–847, 1937.
58. Bull, G. M. Postural proteinuria. *Clin. Sc.*, 7: 77–108, 1948.
59. Rubin, M. I., Bruck, E. and Rapoport, M. Studies of maturation of renal function in normal children and renal functional disturbances during various forms of kidney disease in childhood. *Quart. Rev. Pediat.*, 2: 524, 1947.
60. Schwarz, H., Kohn, J. L. and Weiner, S. B. Lipid nephrosis: observations over a period of twenty years. *Am. J. Dis. Child.*, 65: 355–363, 1943.
61. Peters, J. T. Epicellular and pericellular depositions of amyloid as the starting point of amyloidosis. *Arch. Path.*, 35: 832–835, 1943.
62. Armstrong, J. B. A study of renal function in patients with multiple myeloma. *Am. J. M. Sc.*, 219: 488–493, 1950.
63. Davies, D. F. and Shock, N. W. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J. Clin. Investigation*, 29: 496–507, 1950.
64. Farber, S. J., Conan, N. J., Jr. and Earle, D. P., Jr. Effect of diabetes and insulin on glucose Tm and other renal functions. *Am. J. Physiol.*, 155: 436, 1948.
65. Oliver, J. The morphological aspects of renal tubular secretion and reabsorption. Tr. Josiah Macy Jr. Foundation Conference on Renal Function, 1: 15–62, 1949.
66. Corcoran, A. C., Taylor, R. D. and Page, I. H. Acute toxic nephrosis. *J. A. M. A.*, 123: 81–85, 1943.
67. Redish, J., West, J. R., Whitehead, B. W. and Chasis, H. Abnormal renal tubular back-diffusion following anuria. *J. Clin. Investigation*, 26: 1043–1045, 1947.
68. Sirota, J. S. Carbon tetrachloride poisoning in man. I. The mechanisms of renal failure and recovery. *J. Clin. Investigation*, 28: 1412–1422, 1949.
69. Richards, A. N. Direct observations of change in function of the renal tubule caused by certain poisons. *Tr. A. Am. Physicians*, 44: 64–67, 1929.
70. Corcoran, A. C. and Page, I. H. Renal damage from ferroheme pigments—myoglobin, hemoglobin, hematin. *Texas Rep. Biol. & Med.*, 3: 528–544, 1945.
71. Bing, R. J. The effect of hemoglobin and related pigments on renal functions of the normal and acidotic dog. *Bull. Johns Hopkins Hosp.*, 74: 161–176, 1944.
72. Yuile, C. L., Gold, M. A. and Hinds, E. G. Hemoglobin precipitation in renal tubules. A study of its causes and effects. *J. Exper. Med.*, 82: 361–374, 1945.
73. Clark, J. K., Barker, H. G. and Crosley, A. P., Jr. Evidence against renal vascular shunts in a case of lower nephron nephrosis. *Am. J. Med.*, 9: 268–271, 1950.
74. Lauson, H. D., Bradley, S. E. and Cournand, A. The renal circulation in shock. *J. Clin. Investigation*, 23: 381–402, 1944.
75. VanSlyke, D. D. The effects of shock on the kidney. *Ann. Int. Med.*, 28: 701–722, 1948.
76. Bywaters, E. G. L. and Stead, J. K. The production of renal failure following injection of solutions containing myohaemoglobin. *Quart. J. Exper. Physiol.*, 33: 53–70, 1944.
77. Badenock, A. W. and Darmady, E. M. The effects of temporary occlusion of the renal artery in rabbits and its relationship to traumatic uraemia. *J. Path. & Bact.*, 59: 79–94, 1947.
78. Trueta, J., Barclay, A. E., Daniel, P. M., Frank-

LIN, K. J. and PRICHARD, M. M. L. Studies of the Renal Circulation. Springfield, Ill., 1947. Charles C Thomas.

79. BRADLEY, S. E. Physiology of essential hypertension. *Am. J. Med.*, 4: 398–415, 1948.
80. GOLDRING, W., CHASIS, H., RANGES, H. A. and SMITH, H. W. Effective renal blood flow in subjects with essential hypertension. *J. Clin. Investigation*, 20: 637–653, 1941.
81. CORCORAN, A. C. and PAGE, I. H. Differential diagnosis of terminal glomerulonephritis and malignant hypertension. I. Renal aspects. *Ann. Int. Med.*, 21: 747–764, 1944.
82. CHASIS, H., GOLDRING, W. and SMITH, H. W. Reduction of blood pressure associated with the pyrogenic reaction in hypertensive subjects. *J. Clin. Investigation*, 21: 369–376, 1942.
83. BRADLEY, S. E., CHASIS, H., GOLDRING, W. and SMITH, H. W. Hemodynamic alterations in normotensive and hypertensive subjects during the pyrogenic reaction. *J. Clin. Investigation*, 24: 749–758, 1945.
84. GENEST, J., NEWMAN, E. Y., KATTUS, A. A., SINCLAIR-SMITH, B. and GENECIN, A. Renal function before and after surgical resection of coarctation of the aorta. *Bull. Johns Hopkins Hosp.*, 83: 429–438, 1948.
85. CHASIS, H. and REDISH, J. Effective renal blood flow in the separate kidneys of subjects with essential hypertension. *J. Clin. Investigation*, 20: 655–661, 1941.
86. SMITH, H. W., GOLDRING, W., CHASIS, H., RANGES, H. A. and BRADLEY, S. E. The application of saturation methods to the study of glomerular and tubular function in the human kidney. *J. Mt. Sinai Hosp.*, 10: 59–108, 1943.
87. KLEMPERER, P. and OTANI, S. "Malignant nephrosclerosis" (Fahr). *Arch. Path.*, 11: 60–117, 1931.
88. DEXTER, L. and WEISS, S. Pre-eclamptic and Eclamptic Toxemia of Pregnancy. Boston, 1941. Little, Brown & Co.
89. WELLEN, I., WELSH, C. A. and TAYLOR, H. C., JR. The filtration rate, effective renal plasma flow, tubular excretory mass and phenol red clearance in specific toxemia of pregnancy. *J. Clin. Investigation*, 21: 63–70, 1942.
90. LAMBERT, P. P. Polycystic disease of the kidney, a review. *Arch. Path.*, 44: 34–58, 1947.
91. FRIEDMAN, M., SELZER, A., SUGARMAN, J. and SOKOLOW, M. The renal blood flow, glomerular filtration rate and degree of tubular reabsorption in renal glycosuria. *Am. J. M. Sc.*, 204: 22–24, 1942.
92. GOVAERTS, P. and LAMBERT, P. P. Pathogénie due diabète rénal. *Acta Clin. belg.*, 4: 341–370, 1949.
93. NIELSEN, A. L. On the mechanism of glycosuria, I. *Acta. med. Scandinav.*, 130: 219–231, 1948.
94. HAMBURGER, J. and RYCKEWAERT, A. Nouveaux procédès d'exploration fonctionnelle du rein. Paris, 1949. Flammarion.
95. MCCUNE, D. J., MASON, H. H. and CLARKE, H. T. Intractable hypophosphatemic rickets with renal glycosuria and acidosis (the Fanconi syndrome). *Am. J. Dis. Child.*, 65: 81–146, 1943.
96. ALBRIGHT, F. and REIFENSTEIN, E. C., JR. The Parathyroid Glands and Metabolic Bone Disease. Baltimore, 1948. Williams & Wilkins.
97. UZMAN, L. and DENNY-BROWN, D. Amino-aciduria in hepato-lenticular degeneration (Wilson's disease). *Am. J. M. Sc.*, 215: 599–611, 1948.
98. COOPER, A. M., ECKHARDT, R. D., FALOON, W. W. and DAVIDSON, C. S. Investigation of the amino-aciduria in Wilson's disease (hepatolenticular degeneration): demonstration of a defect in renal function. *J. Clin. Investigation*, 29: 265–278, 1950.
99. WILLIAMS, R. H. and HENRY, C. Nephrogenic diabetes insipidus: transmitted by females and appearing during infancy in males. *Ann. Int. Med.*, 27: 84–95, 1947.
100. CHASIS, H., REDISH, J., GOLDRING, W., RANGES, H. A. and SMITH, H. W. The use of sodium p-aminohippurate for the functional evaluation of the human kidney. *J. Clin. Investigation*, 24: 583–588, 1945.

Combined Staff Clinic

Uric Acid Metabolism and Gout

THESE are stenotyped reports of combined staff clinics of the College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York. The clinics, designed to integrate basic mechanisms of disease with problems of diagnosis and treatment, are conducted under the auspices of the Department of Medicine. The reports are edited by Dr. Frederick K. Heath.

DR. ALEXANDER B. GUTMAN: It is disappointing indeed that in an era when such extraordinary progress has been made in our understanding of so many disease processes so little insight has been gained into the mechanisms of gout. Although the clinical management of gout has been greatly advanced through happy empirical accidents in the development of therapy, it is still not possible to provide satisfactory answers to most of the basic problems of the underlying metabolic disorder. In recent years, however, some progress toward solution of these problems has been made, due largely to the introduction of new methods of investigation particularly in the employment of isotopes. Much of this recent information is not yet directly applicable to the clinical problems of gout but new points of view have already been established and new and promising avenues of approach are already being explored. It is the purpose of this exercise to present current lines of thinking and experiment in this field and to indicate how the modern management of gout has already been greatly influenced by these new developments.

We will begin with a statement of the problem in the form of a brief description of the clinical manifestations of gout. Dr. Boots, who has had a large experience in this field, has agreed to undertake this assignment.

DR. RALPH H. BOOTS: The aphorisms of Hippocrates made numerous references to gout, stating that the disease occurs mostly in the spring and autumn, that women do not have gout (podagra) until the menopause has occurred, that young men do not have the disease until venery is indulged in and that eunuchs are exempt. The first statement has long been accepted but I see as much gout in the summer and winter as in the spring and autumn. Regarding the second remark, it is still generally valid but both Drs. Cecil and Talbott have recently reported cases of gout occurring in females before twenty years of age.

Sydenham's description of his own attack of gout, which appeared in 1683, is a classic and I will read a few lines from it. "The victim goes to bed in good health and sleeps. About two o'clock in the morning he is awakened by a severe pain generally in the great toe; more rarely in the heel, ankle or instep. This pain is like the dislocation of the bones of these parts, and is accompanied by a sensation as of chilly water poured over the membranes of the suffering joint. Then follow chills and shivers, and a little fever. . . . So exquisite is the feeling of the part affected that it cannot bear the weight of the bed clothes nor the jar of a person walking in the room. Hence the night is passed in torture." Garrod describes the patient's pain in the following fashion: "He got up during the night and fell over and fractured the other leg and didn't feel any pain in the other leg because the pain in his toe was so severe." In our experience gout occurs just as frequently in the daytime as at night although perhaps one feels the pain more at night.

Sydenham took comfort in the fact that great kings, generals and philosophers are more liable to the disease and it was called the "disease of kings and the king of diseases." There are very few kings left, which

may account for the fact that the only patient with acute gout in the Arthritis Clinic in this hospital this month was a colored porter.

Garrod states that most of the cases in women are hereditary. On the other hand, it is said that in the degenerate times of the Roman Empire, when women drank as much as men, they appeared to become subject to gout as often as men. Now, if you will lunch in midtown New York and see who does the drinking, you will agree that that is probably an error because it still is true that gout is a disease of men.

In 1797 Wollaston discovered that the chalky deposits (tophi) of gouty subjects consist of uric acid salts. Garrod in 1847 found abnormal amounts of uric acid in the blood by his thread experiment and gave the first scientific approach. Modern advances from the time of Garrod have until recently dealt mainly with better methods for determining uric acid.

Clinically, the striking features of gout are an arthritis, tophi, hyperuricemia and characteristic changes in roentgenograms. With regard to the first manifestation, *arthritis*, acute gouty arthritis is most frequently seen in the feet but may involve any joint, and characteristically responds to colchicine. Scudamore found one or both great toes alone affected in 341 instances of 516 cases; in 373 cases there was involvement of the great toe and some other joint; and in 143 cases joints other than the great toe were involved. Second, there are *deposits of urates* in the tissues, the so-called tophi. These occur in cartilage, bursae, subcutaneous tissue, tendons, bones and kidneys. Dr. McEwen recently described one case with a tophus on the mitral valve. Third, *hyperuricemia* is usually present. Talbott and Jacobson define hyperuricemia as a serum uric acid level above 6 mg. per cent. Fourth, there are typical *roentgenographic changes*. These do not occur in early acute gout but are found in chronic tophaceous gout. In our experience the punched-out areas near the subchondral plate considered characteristic in x-rays of gout are indistinguishable from similar areas seen in rheumatoid arthritis.

Other interesting features which play a part in this disease are (1) *heredity:* some 50 per cent of patients give a history of gout in the father or grandfather. Talbott investigated 136 relatives of 27 gouty patients and 25 per cent of them had high serum uric acid levels. Smyth and Freyberg reported two very interesting gouty families. In one the father had gout; the mother was normal; there were three sons all of whom had gout, and one daughter who was normal. (2) *Sex:* About 95 per cent of all cases of gout occur in males. (3) *Age:* In most cases gout becomes manifest clinically after thirty-five years of age. (4) Much has been written concerning the *role of food and alcohol*. Regarding food, it is said that "most men after 40 eat too much, especially foods high in purines." Dr. McEwen reported experiments with gouty patients in whom he was able to precipitate attacks of gout with both high purine and high fat diets. Probably no amount of food will produce gout in one who has no predisposition to gout. As for alcohol, an old saying is that "in the first half of your life wine goes to your head and in the second half of your life it goes to your feet." Fermented spirits are supposed to be more apt to provoke gout than distilled liquors. It has been reported that the disease is common among brewery workers who indulge in the drinking of large quantities of beer, and that heavy wines are worse than light wines. It was very common among the two-bottle men in England, this referring to a man who consumed two bottles of port and not two bottles of whiskey.

This disease has usually been divided into two phases described under the terms "acute gout" and "chronic gouty arthritis," the former referring to single or recurring acute attacks of gouty arthritis with complete intervening recovery. Such attacks may last from three days to two months depending on how quickly the diagnosis is made and colchicine therapy instituted. These attacks are occasionally preceded by pre-

monitory symptoms such as joint twinges, irritability and indigestion. Chronic gouty arthritis refers to the disease when the joints no longer recover completely, with development of arthritic deformities, tophi and typical roentgenographic changes.

little pain was developing in his right great toe. He immediately took colchicine and the attack was aborted. W. G. had his only attack of gout in 1949 at sixty-two years of age. The left knee was swollen, hot and tender. He was given colchicine and within

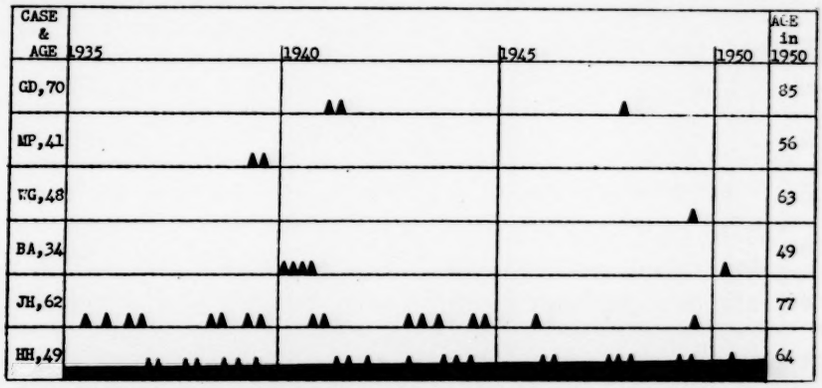


FIG. 1. Natural history of gout in six patients observed over a fifteen-year period. Each peak indicates an attack of acute gout. The heavy black line in Case H. H. indicates presence and slow progression of chronic tophaceous gout.

Some consider that acute gout is simply the first phase of a disease which five to forty years (average twelve years) later develops into chronic gouty arthritis. This view is not substantiated by the clinical course of gout in six patients whom we have followed in office practice for a period of fifteen or more years. (Fig. 1.) Five of these patients presented acute gouty attacks with symptom-free intervals and showed no tendency to develop chronic tophaceous gout. The sixth patient (H. H.) had chronic tophaceous gout when first seen, which continued with occasional exacerbations. In office practice the author has observed acute and chronic gout in a ratio of 4:1.

As indicated in Figure 1, G. D. developed his first symptoms in 1941 at the age of seventy-six years, when he had two attacks of typical acute gout but was free of further trouble until 1948 when he had a single acute gouty attack. In the interval between these three attacks he had no joint symptoms and no tophi have appeared. His hyperuricemia has persisted (7 mg. per cent in 1948). M. P. had two attacks of acute gout affecting his left great toe in 1939. He has had no recurrence from 1939 until the present time although in 1947 he thought a seventy-two hours had entirely recovered. B. A. had four attacks of gout in 1940 and one attack in 1950. J. H. was first seen when sixty-two years of age and has had frequent attacks since that time. On one occasion he had a tophus in his left ear which later disappeared. The left knee, left wrist, left ankle and left and right elbows have been involved in the various attacks. His serum uric acid level continues elevated (8.7 mg. per cent in 1950) but the intervals between attacks are longer than when first seen and there are no residual symptoms between attacks. This patient has been taking colchicine at weekly intervals for ten years. H. H. had chronic gouty arthritis when first seen in 1933. Since that time he has had exacerbations, typical roentgenographic changes and numerous tophi.

Judging by the varied course of these patients, it would seem difficult to prognosticate the future of the patient presenting acute gout.

DR. GUTMAN: We turn now to the metabolism of uric acid and its precursors, a basic aspect of the gout problem. Recent elucidation of this field, a major triumph of the application of isotope technics to biologic problems, has made it clear that uric acid

can be synthesized in the body from simple carbon and nitrogen compounds; it is not derived exclusively or usually even in major part from ingested preformed purines or nucleoproteins.

Dr. Shemin, of the Department of Biochemistry, who has himself made important contributions to this subject, will describe some of the more significant recent developments.

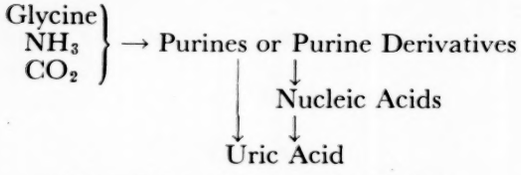


FIG. 2. Scheme for uric acid formation.

DR. DAVID SHEMIN: In man, uric acid is not the main nitrogen excretory product, as in birds and reptiles, but is derived from ingested purine derivatives and from endogenously formed purines. The identification of compounds which may be intermediate in the formation of uric acid is therefore essentially one aspect of the more general problem of the metabolism of purines.

It is now clear that purines and purine derivatives can be synthesized in the body from comparatively simple molecules and that they may be incorporated into nucleic acids or, since formation of nucleic acid is now known not to be an obligatory step, directly oxidized to uric acid. This over-all scheme of uric acid formation may be pictured as shown in Figure 2.

Some of the compounds that are utilized in the biosynthesis of uric acid and other purines have been identified in recent years. It was shown in 1943 by Barnes and Schoenheimer that dietary ammonia is readily incorporated into the purines of the nucleic acids and into uric acid.[1] The compounds which are the source of the carbon atoms of uric acid were identified by Buchanan, Sonne and Delluva.[2,3] The latter investigators showed by use of isotope compounds that carbon atom No. 4 of uric acid (Fig. 3) arises from the carboxyl group of glycine. Since it was later demonstrated that nitrogen atom No. 7 of uric acid is derived from glycine,[4] it may be concluded that the whole molecule of glycine is utilized and occupies the 4, 5 and 7 positions. Indeed, that the No. 5 carbon atom of uric acid arises from the α-carbon atom of glycine was shown by Karlsson and Barker.[5] It was

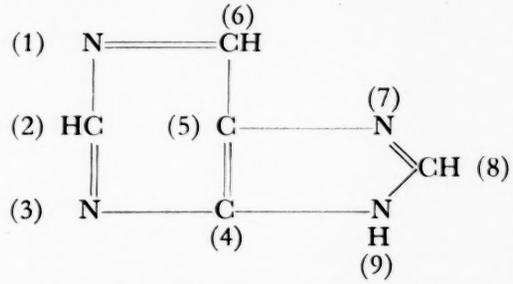


FIG. 3. Purine (numbering system).

further found by the University of Pennsylvania group[2,3] that the source of the uric acid carbon atom No. 6 is CO_2, by perhaps a new mechanism of carbon dioxide fixation, and that the ureide carbon atoms No. 2 and No. 8 are derived from the carbon atom of formic acid. It was subsequently found that the α-carbon atom of glycine also is a good source for the ureide carbon atoms No. 2 and No. 8.[5] This can be explained by the results of Sakami[6] who found that the α-carbon atoms of glycine and formic acid are more or less equivalent for the formation of the β-carbon atom of serine. Therefore, the α-carbon atom of glycine serves as a source of formate or some other one-carbon derivative. The α-carbon atom of glycine has been shown to be important in other biologic systems.

From this brief resumé of the precursors of purines it is evident that glycine, ammonia and carbon dioxide are involved in the synthesis of uric acid and that purine formation is intimately connected with the intermediary metabolism of several comparatively small molecules. Elucidation of the reactions these latter compounds undergo will give further insight into the mechanisms of purine and uric acid formation.

Although the source of each of the atoms of the uric acid molecule is now known with a fair degree of certainty, practically nothing is known concerning any of the

condensation products which may be intermediates. However, a compound has been isolated which presents attractive possibilities as an intermediate. Stetten and Fox[7] found that E. coli under sulfonamide bacteriostasis elaborate a compound which was identified by Shive and co-workers[8] as 5(4)-amino-4(5)-imidazole-carboxamide. (Fig. 4.) It will be noted that if another carbon atom were inserted in position No. 2 of this compound a purine would result. The purine formed would be hypoxanthine or xanthine, depending on the state of oxidation of the carbon atom entering the No. 2 position. Edson, Krebs and Model[9] claim to have demonstrated the synthesis of hypoxanthine in pigeon liver. Indeed it has recently been demonstrated by Schulman et al.[10] that the imidazole carboxamide is converted to hypoxanthine when incubated with pigeon liver homogenate. If hypoxanthine is formed, it may readily be oxidized to uric acid by xanthine oxidase or may be converted to the nucleic acid purines, adenine and guanine.

It is not definitely known whether in the biosynthesis of purines, free purines or derivatives are first formed or whether the endogenous purines are in part directly incorporated into nucleic acids and in part oxidized to uric acid. However, the over-all fate of dietary purines has been investigated. Plentl and Schoenheimer[11] found that on feeding isotopically labeled guanine some of the uric acid excreted was derived from the dietary guanine while none of the guanine of the nucleic acids was derived from the labeled guanine fed. On the other hand, Brown and co-workers[12] found that dietary adenine was converted to uric acid and utilized for nucleic acid formation. In the latter experiment it was found that the uric acid isolated contained a higher isotope concentration than the nucleic acid adenine. This latter finding and the work of Plentl and Schoenheimer would be consistent with the view that free purines can readily be oxidized to uric acid without intermediate incorporation into nucleic acids. It is of interest to note that in the studies on pyrimidines (another base of the nucleic acids) dietary uracil and thymine, as shown by Plentl and Schoenheimer,[11] and cytosine, as shown by Bendich, Getler and Brown,[13] are not incorporated into nucleic acids while cytidine, a nucleotide,

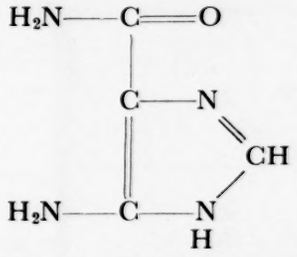


FIG. 4. 5(4)-amino-4(5)-imidazole-carboxamide.

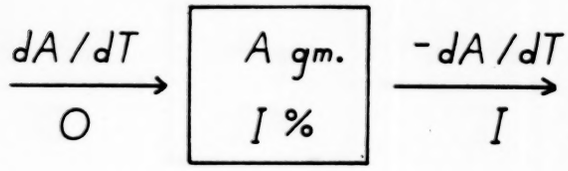
is incorporated into nucleic acids according to Hammarsten et al.[14]

Uric acid can also be formed from the purines of the nucleic acids. There are two types of nucleic acids in the cells, the pentose nucleic acids predominantly found in the cytoplasm and the desoxypentose nucleic acids occurring chiefly in the nuclei. From the studies of Hammarsten and Hevesy[15] and Brown and co-workers[16] it appears that pentose nucleic acids are in the dynamic state, that is they are continuously being broken down and resynthesized, while desoxypentose nucleic acids may not be in the dynamic state. Therefore, the amount of uric acid derived from pentose nucleic acids will be dependent on the turnover rate of these nucleic acids while the amount of uric acid derived from desoxypentose nucleic acids will be a function of the rate of cell formation. It would follow that more uric acid should be formed in such diseases as leukemia and polycythemia vera, which is indeed the case.

In general, then, the amount of uric acid formed in the body depends upon the rate of formation of the purines from their precursors, the availability of the precursors, the amount of direct oxidation of the formed purines, the turnover rates of the pentose nucleic acids of different cells and the rate of regeneration of the cells.

DR. GUTMAN: With this background we can proceed profitably to consideration of

what has long been a central problem in gout: Are the high blood uric acid levels in gout due to *increased production* of uric acid, or to *decreased destruction* of uric acid in the body, or to *impaired renal excretion* of uric acid by the gouty subject? Thus far no



$$K = \frac{dA/dT}{A} = \frac{\ln I - \ln I_o}{T}$$

$$\left(m = \frac{y - b}{x}\right)$$

$$A = a(I_i/I_o - 1)$$

$$dA/dT = KA$$

FIG. 5. Mathematical treatment of isotope dilution method as employed in these studies.

satisfactory answer to this basic question has been forthcoming, largely because adequate methods for measuring the several variables involved were not available. Recently, Dr. Stetten, of the Public Health Research Institute of New York City, developed an elegant technic which can be employed to estimate the rate of production and destruction of uric acid in the body. Drs. Berliner and Yü, of the Columbia Research Service at Goldwater Memorial Hospital, have been applying modern methods of analysis of renal function to the problems of urate excretion by the kidney. These investigators will now present the results of their studies so far and then perhaps we can take stock to see what progress has been made in resolving this basic problem in gout.

DR. DEWITT STETTEN, JR.: The studies[17,18] which I shall describe for you deal largely with a comparison of the rate of uric formation with the rate of its excretion. The first prerequisite for such a study is a sample of isotopic uric acid, which was prepared by methods described elsewhere.[17,19] The isotope selected, because of the necessary use of human subjects in this study, was nitrogen of mass 15. Of the four nitrogen atoms in uric acid, two in the samples synthesized are isotopic, and by starting with the richest source of isotope available to us, some 60 atom per cent of nitrogen, we obtained a material containing approximately 30 atom per cent of isotopic nitrogen. It was obviously desirable to have as high a concentration of isotope as practical in the starting material because by that maneuver we were able to keep the dose of material administered at a relatively low level.

The mathematics which go into such a problem as this are quite simple. (Fig. 5.) The box at the top of Fig. 5 represents what we have termed the 'miscible pool' of uric acid. This is the quantity of uric acid which is capable of prompt mixing with the isotopic uric acid injected intravenously. Its dimensions are in grams or milligrams. If uric acid is entering such a pool at a constant rate and is leaving the pool at the same rate, dA/dT, if it is entering the pool without isotope, mixing thoroughly with the pool, and if the sample of the mixture which is lost in the urine is at all times equal in isotope composition to the instantaneous isotope concentration in the box, one may set up an equation in which the fraction of all of the uric acid in the pool that is replaced by new uric acid per unit time $\frac{dA/dT}{A}$ is equal to $\frac{\ln I_o - \ln I}{T}$. This you will recognize as the expression for a straight line in which $-K$ is the slope of the line and $\ln I_o$ is the intercept of the line when one plots $\ln I$ against T. Once we know the logarithm of the isotope concentration at zero time, the instant of mixing, we can then calculate by the isotope dilution equation the magnitude of the diluent, the miscible uric acid, if we know the quantity injected, a, and the isotope concentration of the material injected, I_i. Knowing A and K we multiply the one by the other to get dA/dT, which is the rate of introduction of new

uric acid into the pool. The validity of the assumptions which were made in this expression is, I think, indicated by the agreement between the experimental points and the derived relationship.

thing obtained in a gouty subject, of whom I shall have more to say later. Again you will notice fairly good concordance between the experimental points and the best straight line that we could draw through them.

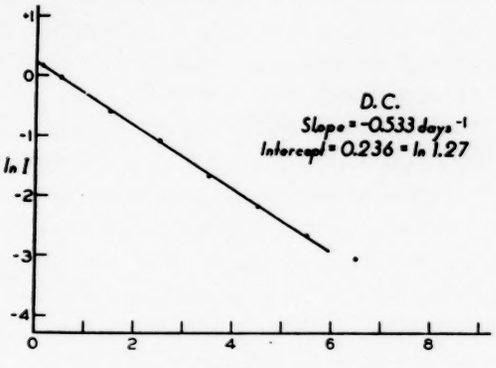


FIG. 6. Normal subject D. C.

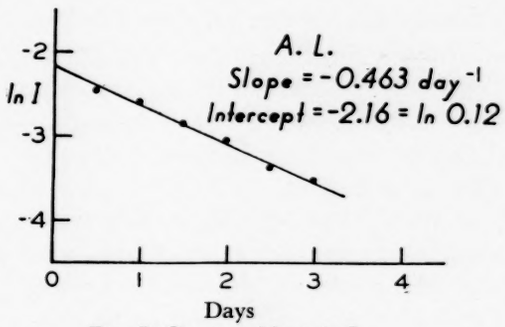


FIG. 7. Gouty subject A. L.

TABLE I

Subject	a = Dose Injected mg.	I_i Injected at. %	I_0 = Antiln of Intercept at. %	A = Miscible Pool mg.	K = Slope day^{-1}	KA = Turnover mg./day	B = Urinary Excretion mg./day	KA-B = Surplus mg./day	C = Body Weight kg.	A/7C = Mean Conc. in Body Water mg. %	Mean Serum Level mg. %
D. C.	59.9	29.7	1.27	1,341	−0.533	715	602	113	73	2.6	6.0
R. B.	56.3	29.7	1.36	1,173	−0.591	693	563	130	62	2.7	6.2
G. W.	75.0	29.6	1.82	1,145	−0.757	867	616	251	76	2.2	4.4
B. S.	111.0	29.7	0.62	4,742	−0.524	2,485	468	2,017	74	9.2	6.9
A. L.	75.0	29.6	0.12	18,450	−0.463	8,530	416	8,114	75	35.1	9.6

Figure 6 shows the results obtained in our first normal human subject. The experimental protocol was very simple. Subjects were hospitalized at the Peter Bent Brigham Hospital under the care of Dr. Peter Forsham and placed on a diet which was virtually devoid of purines for a period of time until the urinary uric acid excretion became quite uniform. While remaining on this diet they received a single injection of isotopic uric acid and from that time forward uric acid was isolated in twelve-hour intervals from the urine and its isotope concentration determined. We have in Figure 6 plotted the logarithm of the isotope concentration against time.

In Figure 7 is shown the same sort of

Table 1 is a summary of the results of the first five experiments that were carried out. The first three subjects (D. C., R. B. and G. W.) were normal medical students and it is evident that the several determinations of the size of the miscible pool of uric acid in normal human males fall fairly close to each other, averaging around 1,200 mg. In other words, in a normal human medical student there are about 1,200 mg. of uric acid capable of prompt and immediate mixing with intravenously injected uric acid. Between 50 and 75 per cent of all the uric acid in this pool is replaced by new uric acid each day, representing 700 to 850 mg. of new uric acid entering the pool daily. In every case these figures were in excess of the

quantity of uric acid excreted in the urine. Since we had no reason to suppose that these subjects were accumulating uric acid, we were forced to the conclusion that they were disposing of uric acid by methods other than urinary excretion. The excretion in feces and sweat was not investigated by us. Fecal losses have been reported by others and may contribute to the surplus. We did find small though significant concentrations of isotopic nitrogen both in the urinary urea and urinary ammonia of most of our subjects, indicating that there is some degree of degradation of uric acid.

The next thing that was done with these figures was to take the quantity of uric acid in the pool and divide it uniformly among all the water that was calculated to be contained in the bodies of these subjects. We obtained the figures in the next to the last column which are the calculated mean concentrations of uric acid throughout all the body waters. You will note that in every case these numbers are approximately 50 per cent of the serum uric acid levels which were obtained in these same subjects, leading to the inference that there are waters in the body poorer in uric acid than the serum.

The last two lines of Table 1 refer to two subjects suffering from gout. The first subject, B. S., had had attacks of acute gout in the preceding two years. He had had one attack of acute gout two weeks prior to the experiment but at the time of the experiment was free of any gross manifestations of the disease. No tophi had been discovered and he was free of symptoms. The serum uric acid was somewhat higher than what is taken as the normal maximum at the Peter Bent Brigham Hospital. His pool of miscible uric acid, determined by the dilution of isotopic uric acid, was approximately four times normal. The last line represents the goutiest man in Boston, so I am assured. This patient has had severe tophaceous gout for at least twenty-five years. He has on three occasions been subjected to surgical excision of tophi in order to give him some degree of joint mobility. His dietary history, whether relevant or not, is bizarre. He was for years the maitre d'hotel of one of Boston's more fashionable hotels and was assigned the responsibility of preparing the canapes and hors d'oeuvre. Paté de foie gras, caviar and sardines featured largely in his diet. His pool of miscible uric acid came out to be about 18,000 mg., which is approximately fifteen times the normal value. His serum uric acid was high, approximately twice the normal value but did not reflect the enormous size of the pool of miscible uric acid. When we divided this much uric acid among all the water which was contained in his body we came out with a value of 35 mg. per cent. This is in excess of the stated concentrations of uric acid achievable in body fluids at saturation. We therefore concluded provisionally that a portion of these 18 gm. of uric acid did not reside in solution in body water at all but represented some of the solid phase urate which this man had in abundance. It certainly did not represent all of his solid phase urate in view of clinical estimates that he probably had several pounds of tophi which he was carrying around with him.

Having obtained these figures, we went back to restudy this man under other circumstances and in Figure 8 is shown the result of another study of this very gouty subject after a period of approximately six months, during which he was out of the hospital and received no consistent treatment. During the month preceding this experiment he received no treatment whatsoever. As soon as we had obtained enough points to lead us to think that we would be able to draw a straight line, we gave this man ACTH. Following administration of the drug his urinary uric acid increased, as was expected, he had a satisfactory uric acid diuresis for the two days of administration and his serum uric acid fell. There was no change in the rate of decline of isotope concentration to which we care to attach any significance. We therefore provisionally suggest that the uric acid diuresis which was observed was not on the basis of the generation of excessive amounts of uric acid

but due rather to interference with tubular reabsorption of uric acid at the renal level, and increased clearance of uric acid from the blood. This man was then discharged from the hospital on 2.4 gm. of aspirin daily. He was left on this regimen for three months, at the end of which time he returned to the hospital with symptoms suggestive of salicylism. During this interval he was spot-checked on two or three occasions and it was observed that his urinary uric acid excretion was approximately 300 mg. per day in excess of his basal urinary uric acid excretion. At the end of this time he was re-hospitalized and a third experiment, shown in Figure 9, was carried out. In order to complete the picture of the therapeutic agents that are most frequently employed, in the middle of this experiment the man was given colchicine for two days. There was no change in either his plasma uric acid level or in his urinary uric acid level. There was no apparent change in the isotope data incident to the administration of colchicine.

The experiments on this one subject with marked tophaceous gout are summarized in Table II. The results in the first experiment we have already discussed. After six months with little therapy the quantity of uric acid in his miscible pool had increased to a matter of 31,000 mg. (experiment 2) which is about twenty-five times the normal value. Observe that the serum uric acid levels had not changed significantly. After a course of salicylates this quantity fell rather dramatically to 2,000 mg., one-fifteenth of its previous value (experiment 3). This figure is but slightly above the normal values we had obtained of about 1,200 mg.

With these large variations it becomes a

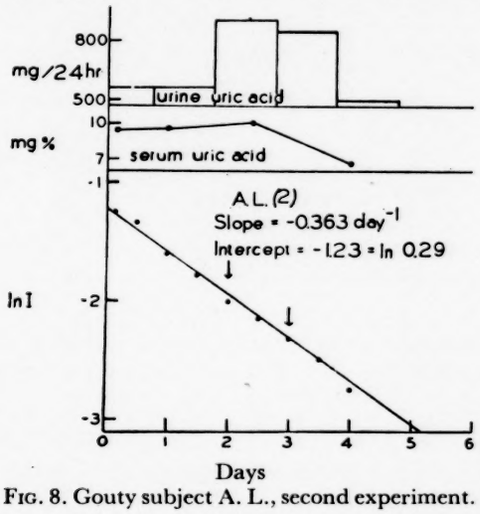


FIG. 8. Gouty subject A. L., second experiment.

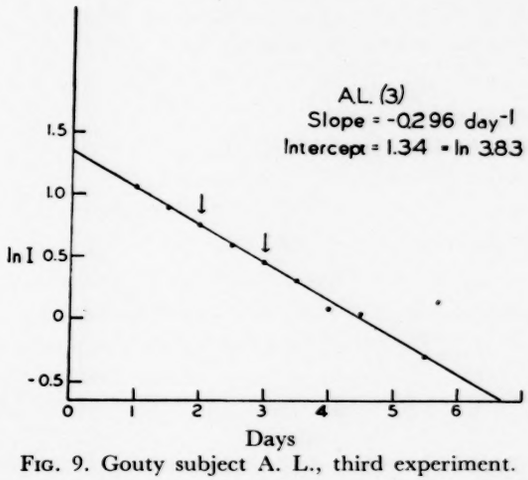


FIG. 9. Gouty subject A. L., third experiment.

TABLE II

INJECTION OF ISOTOPIC URIC ACID INTO GOUTY PATIENT A. L.

Experiment	a = Dose Injected mg.	I_i Injected at. %	I_0 = Antiln of Intercept at. %	A = Miscible Pool mg.	K = − Slope day^{-1}	KA = Turnover mg./day	B = Urinary Excretion mg./day	KA − B = Surplus mg./day	C = Body Weight kg.	A/7C = Mean Conc. in Body Water mg. %	Mean Serum Level mg. %
1	75.0	29.6	0.12	18,450	0.463	8,530	416 ± 8	8,114	75	35.1	9.6 ± .1
2	306	29.6	0.29	31,019	0.363	11,259	*		75	59.1	9.5 ± .1
3	300	30.4	3.82	2,084	0.296	200	323 ± 34	−123	75	3.9	10.2 ± .1

* Due to injection of ACTH urinary uric acid values were inconsistant.

matter of some interest to find out something more about the boundaries and the compartments of this pool of miscible uric acid. To explore this we made one further assumption which is demonstrated in Table III. These are data which were obtained in our normal subjects. We have, on the assumption that there is some 5 per cent of body weight in the form of plasma, calculated the quantity of uric acid which is present in the plasma of these subjects. This quantity we have in each case deducted from the miscible pool and the difference we believe to represent uric acid present in the miscible pool but not included in the vascular tree. Dividing the one quantity by the other, we get a ratio which represents the distribution of uric acid on both sides of the vascular membrane, and this ratio we believe is sufficiently uniform to warrant its use in the interpretation of our data secured from gouty subjects. In other words, we have made the assumption that there is about 5.2 times as much uric acid in solution outside of the vascular tree as there is inside of the vascular tree and suggest that the disease gout probably does not disturb this distribution insofar as it is determined by the relative volume of water in these two compartments and by Donnan membrane equilibrium forces.

TABLE III
QUANTITIES OF RAPIDLY MISCIBLE URIC ACID IN FLUID COMPARTMENTS OF NORMAL MEN

Subject	A In Total Pool mg.	B* In Plasma Water mg.	A − B = C In Non-plasma Water mg.	Ratio C/B
D. C.	1,341	224	1,117	5.0
R. B.	1,173	196	977	5.0
G. W.	1,145	171	974	5.7
Mean	1,220	197	1,023	5.2

* Taking plasma equal to 5.1% of body weight.

Applying this figure to data secured from gouty patients, we have calculated the values shown in Table IV. These are four experiments on the two gouty subjects and here we have the amount of uric acid in the plasma, the amount of uric acid computed to be in solution outside of the plasma, and the residue; and provisionally we would like to suggest that this residue represents uric acid as solid phase urate which is still in a condition to be promptly miscible with the uric acid in solution. B. S. is the mildly gouty man, A. L. is our severely gouty man; 1—as first seen, 2—after an interval with no treatment, and 3—after intensive salicylate therapy. The quantity which accounts for the wide fluctuations noted in the period without therapy and the period after therapy is the uric acid which we believe to be present in the solid phase. In patient A. L. this value rose from 16 to 29 gm. in the first interval and fell essentially to zero on salicylate therapy.

TABLE IV
DISTRIBUTION OF RAPIDLY MISCIBLE URIC ACID IN GOUTY PATIENTS

Subject	A In Total Pool mg.	B In Plasma Water mg.	C = 5.2B In Non-plasma Water mg.	A − (B + C) In Solid Phase mg.
B. S.	4,742	261	1,355	3,126
A. L. (1)	18,450	352	1,830	16,270
A. L. (2)	31,019	371	1,929	28,719
A. L. (3)	2,084	382	2,008	(−306)

The final experiment which we did was, unfortunately, in retrospect something of a blunder. We wanted to obtain a tophus in the middle of such an experiment but this was deferred until the last experiment and obviously we could not expect to find much isotopic urate in the solid phase in the last experiment. We thought that we might be able to peel this tophus much as one can shell a pearl and in this way determine the isotope abundance in the uric acid of the several laminas. Unfortunately, tophi are not like that, so we did the best we could. We placed the tophus in a Soxhlet extractor and extracted serially with boiling water. (Table V.) These are three successive extracts from the same tophus. Recorded are

the amounts of uric acid which were obtained in each succeeding extract and the concentrations of N^{15} in the uric acid of each extract. The latter values did decline serially, implying that the uric acid which was secured in the first extract represented the uric acid which had been deposited most recently. However, the values are extremely low as compared with the concentration of isotope which we believe to have been present in the plasma at that time.

TABLE V
N^{15} IN TOPHUS URIC ACID

Extract No.	Uric Acid Extracted mg.	N^{15} Atom %
1	240	0.019
2	705	0.014
3	465	0.006

Tophus, 6.82 gm. dry wt., excised on 9th day, exp. A. L. (3), N^{15} in pool (extrapolated) = 0.27 atom %.

We interpret our results to mean that there is a pool of uric acid in the body which mixes promptly with intravenously injected uric acid; that included in this pool in the gouty subject is a portion of the urate which is present in the solid phase; that in the patient suffering from very long-standing chronic tophaceous gout, not all of the urate in the solid phase is thus included. It is not too difficult to imagine that the urate which has been most recently precipitated, which is still in contact with body water and perhaps in a microcrystalline form, is capable of prompt re-solution and reprecipitation whereas the dry, chalky deposits which are seen in the centers of old tophi, being in contact with no fluid whatsoever, are incapable of solution under any circumstances.

DR. GUTMAN: Was there any visible change in the size of the tophi in the patient with severe tophaceous gout who first showed a very marked increase in the miscible pool and then a very marked decrease in the miscible pool?

DR. STETTEN: No, there was no gross change but a change of 12 or 15 gm. of uric acid would, I think, not have been noted clinically in this subject. He has enormous excrescences on his elbows, ankles, wrists and feet.

STUDENT: Isn't it likely that the uric acid deposits in tophi would not be readily miscible with injected labeled uric acid and so not be included in the miscible pool? The miscible pool therefore probably would not include the uric acid in tophaceous deposits.

DR. STETTEN: I think that is very likely and, as I pointed out, the amount of N^{15} labeled uric acid actually found in the tophus examined was very small.

DR. GUTMAN: We encounter a similar difficulty in chronic tophaceous gout treated with various uricosuric agents. Although some of these agents produce a large increase in the excretion of uric acid in the urine which can be maintained for months, we rarely observe any definite decrease in the size of tophi. Apparently the uric acid deposits in large tophi are beyond the reach of humoral agents and are not in equilibrium with the plasma uric acid.

The second question I want to ask, Dr. Stetten, concerns the finding of N^{15} in the urinary urea and ammonia. This implies some destruction of uric acid in the body. Was that your interpretation?

DR. STETTEN: Yes. But in view of the recent findings of Geren et al.[20] who recovered large amounts of isotope in urea after oral administration of uric acid one must entertain the possibility that the decay of uric acid is a function of the intestinal flora.

DR. GUTMAN: I bring that out because our information as to whether uric acid is destroyed in the human body is, as yet, very meager. Uricase has not been found in human tissues.

DR. AARON BENDICH: In our studies at the Sloan-Kettering Institute referred to by Dr. Stetten we gave a normal individual some labeled uric acid by mouth and found that about half of the uric acid was oxidized to urea and ammonia. We could recover only about one-fourth of the labeled uric acid in the urine. However, using the same

normal subject, when the same amount of uric acid subsequently was injected intravenously we could find no evidence whatever of any degradation of uric acid. We could isolate approximately 85 per cent of the injected uric acid as such. The urea

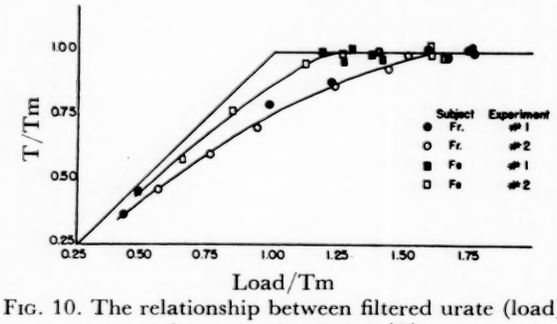


FIG. 10. The relationship between filtered urate (load) and urate reabsorption (T).

and ammonia recovered from the urine did contain very small amounts of isotope but we have subsequently discovered that even in normal individuals not given any isotopic supplement the urinary urea and ammonia contain very small amounts of N^{15}. In our experiments, therefore, we obtained no evidence of oxidation of uric acid in man except when uric acid is fed by mouth; then there is extensive breakdown of uric acid in the alimentary tract, presumably by the bacteria of the gut.

DR. GUTMAN: And now, Dr. Stetten, will you tell us whether your experiments indicate increased formation of uric acid in gouty subjects?

DR. STETTEN: It is not possible to state whether the accumulation of uric acid in gout results primarily from excessive rate of formation or deficient elimination from the pool. Our results to date give no positive indication of disturbance either of ingress to or egress from the pool in this disease. In view of the slowness of the process of accrual of uric acid, it is not altogether surprising that its mechanism should prove elusive.

DR. GUTMAN: Perhaps another approach to the problem, study of the renal excretion of urate in gout, will give us additional information on this point.

DR. ROBERT W. BERLINER: In considering the part played by the kidney in gout we are dealing with a twofold problem. The first concerns the role of the kidney in establishing the elevated uric acid level in the plasma, which we may assume is one of the essential features of the disease; second, the effect of the elevated plasma urate concentration on the kidney and the extent to which secondary renal damage may contribute to further progression of the disease.

We might begin by examining the background against which an evaluation of urate excretion must be made, the renal processes by which urate is excreted. The first problem in this regard is how much urate is filtered at the glomeruli. Opinion on this point is divided but the available evidence[21] would appear to favor the view that practically all the urate in plasma is in filterable form and that the amount of urate filtered can be considered to be the product of filtration rate and plasma urate concentration. This, in a normal human subject of average size, would mean that 5 or 6 mg. of urate are filtered each minute. Something under 10 per cent of this amount normally is excreted in the urine. Obviously there must be some mechanism for reabsorbing urate from the tubular urine.

Some confusion as to the nature of this reabsorption mechanism has arisen. When the urate concentration in plasma is moderately elevated by artificial means the fraction of the filtered urate which appears in the urine is not much increased. However, we have found[21] that if the urate concentration is pushed up far enough, a somewhat different result is obtained as shown in Figure 10. Here the amount of urate reabsorbed by the tubules is plotted against the amount filtered. It can be seen that as the amount filtered is increased the amount reabsorbed also increases, up to a point beyond which no further increase in the amount reabsorbed occurs. In other words, there is a maximum tubular transport capacity, a Tm, for uric acid. The magnitude of the Tm, which in the few we have measured averages about 15 mg./minute, is not shown in the figure. This value is so large that the Tm is not saturated until the

plasma urate increases to at least 15 mg. per cent; in other words, it is never saturated in the normal individual.

In Figure 10 the points at the left represent the normal excretion of urate. The factors which determine how far these points fall below the diagonal line, in other words, the factors which determine the amount of urate excreted, have not been elucidated in normal man and are even more obscure in the patient with gout. In gout, moreover, we have the additional complicating factor of secondary impairment of renal function which would make comparison with urate reabsorption in the normal individual especially difficult.

So much for a background of what is known concerning the mechanisms for excreting urate. Fortunately, a complete understanding of these mechanisms probably would not be essential to clarification of our primary problem—the cause of the elevated plasma urate in gout. As has been pointed out, the possible causes are (1) increased production of urate, (2) impaired excretion by the kidney and (3) decreased destruction in the body. Since, as has been indicated, the normal destruction of urate accounts for such a small part of the total urate turnover, the problem devolves upon the question of whether or not the rate of urate production in gout is increased. If the rate of production is *not* increased, the primary abnormality can be only renal. If the rate of production *is* increased, we may presume that the kidney plays only a secondary role. Now one point in this connection is often misunderstood. I should like to make it clear that excretion of a normal or even of an increased amount of urate in the urine does not mean that the kidney excretes urate normally. As an example, when renal function is impaired there is not a continued decrease in the excretion of urea. The daily excretion of urea parallels the rate of production. The diminished capacity to clear the blood of urea is manifested by an elevated concentration in the blood, not by a decrease in urinary excretion. So conclusions about the state of the renal mechanism for excreting urate cannot be based, as is so often done, on the concentration of urate in the urine or on the total twenty-four-hour excretion.

Ordinarily, when faced with the problem of whether or not the production of some waste product is increased, we would place a series of patients on some standard diet and compare the daily output with that of a series of normal subjects. In the case of urate this would probably give us a fairly satisfactory estimate of urate production in the normal individual, perhaps allowing for a small amount destroyed in the body. In the patient with gout, on the other hand, there is no assurance that this would be true. The reason for this is apparent from the data presented by Dr. Stetten, namely, that in the gouty individual there appears to be an appreciable pool of urate which is in equilibrium with the urate of the body fluids and which can be added to or drawn upon. Only if we had some assurance that this pool, to say nothing of the urate deposited in tophi, were constant could we suppose that the urate excreted by the gouty patient corresponds to the urate actually produced during the period of study.

Entirely apart from these considerations there are very few data available on the amount of urate excreted in gout. Dr. Yü will tell us more about this aspect of the problem.

Whatever may be the primary cause of the elevated urate in gout there can be no question that gout frequently causes progressive impairment of renal function. This is not primarily the result of urate calculi, which of course may further impair renal function, but is probably due to the deposition of urates in the renal parenchyma. The impairment of renal function probably results in further elevation of the plasma urate and contributes to the tendency for urate to be deposited in the body.

In summary, we are not in a position to give a definitive answer to the question of the primary metabolic defect in gout. The data available suggest that it is more likely an increase in urate production than a

primarily renal abnormality but this is by no means certain. Further clarification would seem more likely to result from precise determination of the rate of urate formation than from further studies of the renal excretion of urate.

Dr. T. F. Yü: The general impression given in the literature on gout is that the urinary uric acid excretion of the gouty subject is not greater than that of normal man but is usually within normal limits and often depressed. This impression is based on relatively few studies. More recent investigation does not altogether conform with this view. Talbott and Coombs[22] observed two relatively young gouty subjects who excreted more than 2 gm. of uric acid a day on a low purine diet. Brøchner-Mortensen[23] found a mean urinary uric acid excretion of 414 mg. per day in eleven patients with gout (range 297 to 680 mg./day) as compared with a mean of 374 mg. per day in twenty normal persons (range 269 to 532 mg./day). Friedman and Byers[24] have recently emphasized that the urinary excretion of uric acid in relatively young gouty subjects tends to exceed the normal; the mean daily excretion in five such patients was 567 mg. as compared with a mean of 390 mg. in six normal persons.

Our own data include observations in thirty-one patients with gout (mean age fifty-three years) and in ten non-gouty control subjects (mean age fifty years) all of whom were on a protracted low-purine, low-protein diet restricted to dairy products, cereals, vegetables and fruits. The determinations of uric acid were made by a modification of the method of Buchanan, Block and Christman incorporating the use of uricase, urea cyanide-carbonate and arsenophosphotungstic acid. Urine samples were collected for three or four days The mean twenty-four-hour urinary excretion of "true" uric acid in the gouty subjects was 523 $\pm$ 169 mg. as compared with 424 $\pm$ 73 mg. in the non-gouty group, a difference of borderline significance. The most obvious factor affecting the amount of uric acid excreted appeared to be the state of renal function. In thirteen of our gouty patients with apparently unimpaired renal function, as indicated by serum NPN, PSP excretion test and routine urine analysis, the mean daily urinary excretion of "true" uric acid was 614 $\pm$ 162 mg., significantly above the normal; whereas in eighteen gouty patients with more or less overt renal damage the mean figure was 457 $\pm$ 143 mg., not significantly different from that of the control group. In three cases with marked impairment of renal function the urinary excretion of uric acid was unequivocally reduced, to 190–304 mg. per day. This distribution is shown in Figure 11.

Dr. Gutman: If on a low purine diet the excretion of uric acid is distinctly increased in gout before overt renal damage occurs, and hyperuricemia nevertheless is consistently maintained, the most reasonable conclusion that can be drawn in the light of present knowledge is that excessive production of uric acid occurs in some gouty patients. Impairment of renal function, which frequently occurs, would secondarily aggravate renal retention of uric acid.

Dr. Franklin M. Hanger: There has been a great deal of discussion about uric acid in this clinic on gout but I would like to know whether uric acid really has anything to do with gout, at least with acute gout.

Dr. Gutman: Dr. Hanger, you raise a point which is coming to the fore more and more in the minds of many students of gout. Everyone will concede that chronic tophaceous gout obviously is due to deposition of uric acid or salts of uric acid. There are, however, many reasons to doubt that uric acid *per se* is immediately concerned with the symptoms of acute gout. From all indications, uric acid is a physiologically inert substance. Acute gouty arthritis does not occur in many patients with sustained and marked hyperuricemia (for example, in uremics), though hyperuricemia is almost always present in untreated acute gout. Uric acid fed by mouth, injected by vein or injected into joints and tissues will not cause acute gout either in the normal or

gouty subject. It is a common clinical observation that an acute gouty attack usually occurs in joints that do not show large deposits of urates in roentgenograms and as more and more urate is deposited in and around that joint acute attacks are apt to migrate to other joints relatively free of urate deposits. There is usually no significant change in the serum level or urinary excretion of uric acid just prior to, during or following an untreated acute attack of gout; and remission induced by colchicine also is not associated with any significant change in serum or urinary uric acid. Uricosuric agents (except ACTH and cortisone) do not convincingly prevent or abate acute attacks of gout in spite of the marked increase in urinary excretion and decrease in serum uric acid they may produce; in fact, we have encountered apparent precipitation of acute gout associated with a vigorous increase in urinary uric acid excretion. In the case of ACTH or cortisone, there is no correlation between the degree of amelioration of symptoms in acute gout and the uricosuric effect of these agents; we have observed a marked uricosuric effect produced by ACTH with little or no clinical response.

It seems to me more reasonable to suppose that some precursor of uric acid rather than uric acid itself is responsible for acute gouty attacks.

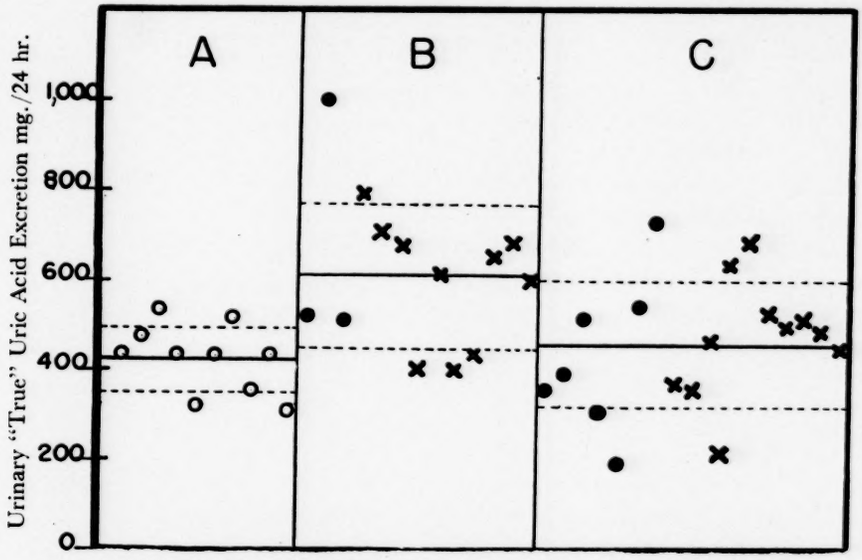


FIG. 11. Comparison of urinary uric acid excretion in gouty and non-gouty individuals on a constant low purine, low protein diet. In each category the solid line represents the mean; broken lines indicate standard deviation. A, ten non-gouty control subjects; B, thirteen patients with gout without overt renal damage. Solid dots represent cases with extensive tophaceous gout; crosses represent cases with few or no tophaceous deposits. C, eighteen patients with gout and overt renal damage. Solid dots represent cases with extensive tophaceous gout; crosses represent cases with few or no tophaceous deposits.

DR. ROBERT F. LOEB: Gudzent and others have suggested that there may be an allergic basis for acute gout, particularly in those gouty individuals who seem to be especially prone to attacks after eating specific foods or taking certain wines. Has any progress been made in clarification of that concept?

DR. GUTMAN: There are many things about an acute attack of gout that resemble allergic phenomena and I have no doubt that in a sensitized person who also has gout the stress of an allergic reaction may precipitate acute gout. Whether the relation of acute gout to allergy is closer than this has not been made clear. Attempts to alleviate acute gouty attacks with antihista-

minics such as pyribenzamine have been unsuccessful in our hands.

I should like at this point to go on to a consideration of the management of gout. For this purpose it is helpful to separate the problem of acute gout from that of chronic gouty arthritis even though the two problems often overlap. The mainstay of *treatment of acute gouty arthritis* is still colchicine, which is given in divided doses to the point of diarrhea, nausea or vomiting in the manner with which you are all familiar. What is not so well known is the growing conviction that colchicine has a pre-eminent place also in the *prophylaxis* of acute gout when there is frequent recurrence of attacks. In our experience in twenty-three such cases the regular ingestion of colchicine has proved to be by far the most effective method of minimizing the frequency and intensity of acute gouty attacks; in some instances this has made the difference between virtual incapacitation and relatively normal activity. The patients regularly take colchicine, usually every night or every other night in doses of 0.5 or 1.0 mg., occasionally more in very severe cases, according to their requirement. They are taught also to take larger, abortive doses of colchicine upon the first intimation of an attack when there is warning pain, stiffness or other indisposition. Adjuvant analgesics, particularly salicylates, are employed especially when residual stiffness of joints is present.

ACTH, in divided daily doses of 50 to 100 mg., and cortisone, in doses three or four times that amount, also have an important place in the treatment of acute gouty arthritis, usually eliciting rapid and marked remission. These agents may be effective in the occasional patient who responds slowly and incompletely to colchicine. On the other hand, they may be ineffective in patients who do well with colchicine; consequently some physicians now treat acute gout with both colchicine and ACTH or cortisone, continuing administration of colchicine for some time after the acute symptoms have subsided in order to prevent recurrence upon discontinuance of ACTH or cortisone. In our experience[25] such exacerbation of symptoms immediately following remission of an acute attack usually is attributable to inadequate or insufficiently prolonged administration of ACTH and we find that provocation of an acute attack by ACTH in interval gout is the exception rather than the rule.

The *management of chronic gouty arthritis* has been the subject of comparatively little controlled investigation, presumably because the slow and insidious development of tophaceous deformity and crippling arthritis is not as arresting a phenomenon as are the spectacular manifestations of acute gout. The problem here is to minimize the deposition of urate when the rate of formation greatly exceeds the rate of elimination, and to mobilize such deposits once they are formed. Two methods of attack are available, first to restrict the diet so as to reduce the intake of uric acid precursors, an approach which has the severe limitations I shall consider subsequently; and second to increase the excretion of urate by uricosuric agents, the effects of which Dr. Yü and I have been studying systematically. We began with salicylates, long known as an effective uricosuric agent when given in sufficiently large dosage and particularly when combined with alkalinizing salts. The mean increase in urinary uric acid excretion (corrected for gentisic acid and other non-urate chromogens) in seven gouty patients given 1.3 gm. aspirin 4 i.d. together with 5.0 gm. sodium bicarbonate daily was 79 per cent. This was associated with a sharp drop in serum uric acid. This response would be highly satisfactory but unfortunately such a high dosage could not be maintained for more than a few consecutive days in the older age group represented by our gouty patients because of the development of tinnitus, confusion, gastrointestinal symptoms and other indications of salicylism. Smaller doses of aspirin, such as 3.0 gm. daily, were found to have no significant uricosuric effect in most patients.

On the basis of a report by Wolfson and

associates[26] that carinamide (4′-carboxyphenylmethanesulfonanilide) increases uric acid excretion in normal subjects, this drug was tried in thirteen gouty subjects. On a daily dosage of 12 to 13.5 gm. the mean increase in urinary uric acid excretion was 61 per cent, associated with a marked and sustained fall in the serum uric acid level. Administration of this drug could be maintained for weeks or months but the large number of tablets consumed daily was objectionable and a variety of reactions—gastrointestinal symptoms, drug fever, drug rash—developed in some instances. More recently we have been using a compound structurally related to carinamide, Benemid,* p-(di-n-propylsulfamyl)–benzoic acid, in divided daily doses of 2.0 gm. The mean increase in urinary uric acid excretion in fourteen patients was 58.5 per cent, associated with a sustained fall in serum uric acid to approximately half the initial level. Reactions to protracted administration were of the same character as with carinamide but were less marked and frequent. Smaller doses of 1.0 gm. daily also are effective and produce fewer reactions. Although more experience is required, Benemid appears to be the most satisfactory uricosuric agent yet tested, except for an apparent propensity to provoke acute gout in some patients who require covering doses of colchicine. From present indications its usefulness as a uricosuric agent depends upon effective and fairly selective suppression of tubular reabsorption of urate.

We come now to the controversial question of dietary restriction in gout. There is no altogether convincing evidence, as yet, as to the efficacy of severe restriction of purine, protein or alcohol intake. It is clear, however, that less uric acid is excreted in the urine when exogenous sources of preformed purines are limited. It is reasonable to suppose, therefore, that less uric acid is retained in the body, particularly when renal excretion is impaired, if the purine intake is low. However, it is now also clear that ingested preformed purines are by no means the only source of uric acid and purine intermediates since these are synthesized in the body at a vigorous rate from the simplest carbon derivatives of carbohydrate and fat and from nitrogen derived from all protein sources. Complete control of uric acid formation by dietary regulation is therefore obviously impossible.

In this dilemma the most feasible approach would seem to be restriction of the protein as well as purine intake and for some years I have been using such diets in the management of patients subject to frequent attacks of acute gout and in patients with chronic gouty arthritis. The results are inconclusive. Attacks of acute gout are not precluded by rigid dietary restriction alone although I have the definite impression that they diminish in frequency and intensity. In chronic gouty arthritis there appears to be less stiffness and disability and most of my patients have voluntarily continued to adhere more or less closely to their onerous low-protein, low-purine diet on that account. This kind of evidence is unsatisfactory, however, and it is to be hoped that the new technics made available by Dr. Stetten will make more precise measurement possible.

STUDENT: How does colchicine exert its effects in acute gout?

DR. GUTMAN: No one knows. Judging from the minute amounts required my guess is that colchicine acts upon some enzyme system, presumably one associated with the intermediary metabolism of purines.

STUDENT: Is gout caused by some derangement of the "pituitary-adrenal axis"?

DR. GUTMAN: I do not believe that the available evidence justifies that view. Any such conclusions based upon the effects of ACTH and cortisone in gout would seem to be premature in view of the wide diversity of disorders favorably affected by these agents.

SUMMARY

DR. GUTMAN: Gout is a disorder of purine metabolism characterized by hyperuricemia and recurrent acute arthritis, often eventu-

* We are indebted to Sharp and Dohme for a generous supply of this drug.

ally associated with urate deposits in the tissues which may be manifest as tophi or as typical roentgenographic changes. The natural history of the disorder is generally divided into two phases: "acute gout," the period of single or recurring acute attacks of gouty arthritis with complete freedom of symptoms between attacks; and "chronic gouty arthritis," when the interval between acute attacks no longer is symptom-free but is characterized by progressive disability due to stiffness and deformities of joints, and the appearance of tophi and typical roentgenographic changes. The course of the disease is variable, however, and many patients with acute gout do not, even upon observation for many years, develop the manifestations of chronic gouty arthritis.

An important recent development is the realization that uric acid is derived not only from ingested preformed nucleoprotein or purine but is synthesized within the body at a vigorous rate from the simplest carbon and nitrogen compounds. It has been established by isotope studies that glycine and ammonia contribute nitrogen to the formation of uric acid and that the carbon atoms are derived from formate, glycine and carbon dioxide. Evidently, ingested carbohydrate, fat and proteins, as well as preformed purines, all must be considered to be precursors of uric acid. It has also been shown that incorporation into nucleic acids is not an obligatory step in the biosynthesis of uric acid.

Another important advance in elucidation of the mechanisms of gout is the development of a method for estimating the turnover rate and extent of the miscible pool of uric acid. This is accomplished by measuring the rate of dilution of N^{15}-labeled uric acid after intravenous injection. The method has already revealed that in the normal subject some 700 to 850 mg. of uric acid is formed daily; it has not yet been established whether or not the rate of production of uric acid is excessive in the gouty patient, an important point. It has been demonstrated further that the miscible pool of uric acid is increased in gout, even when uric acid deposits are not clinically or roentgenographically apparent. The method offers a means of measurement of these deposits although a serious limitation derives from the circumstance that the uric acid incorporated into tophi probably does not mix readily with the injected labeled uric acid, hence is not included in the miscible pool. Finally, additional evidence has been provided that uric acid is not degraded to any significant extent in man.

With regard to the role of the kidneys in gout, several important advances have been made. A maximum tubular transport capacity, Tm, has been established for uric acid in normal man, indicating an "active" (enzymatic) tubular transporting mechanism of limited capacity. The tubular capacity for reabsorption of urate is large, however, in excess of any load that would be imposed even in gout. Of further significance are recent data indicating that many patients with gout excrete greater than normal amounts of uric acid so long as kidney damage, as measured by the ordinary laboratory criteria, is not appreciable.

It is not yet possible to state definitely whether the hyperuricemia of gout is due to increased production of uric acid, decreased destruction of uric acid or impaired renal excretion of uric acid. The available evidence suggests, however, that increased production of uric acid occurs at least in some instances, in which it appears to be a primary factor. Impaired renal excretion of uric acid is an important secondary factor which in many cases contributes significantly to hyperuricemia, particularly in the later phases of gout.

In the management of gout the mainstay of treatment of the acute gouty attack is still colchicine, with ACTH and cortisone as additional effective agents. In patients subject to frequent bouts of acute gout colchicine should be taken regularly as an important prophylactic agent. When there are indications of the development of chronic gouty arthritis uricosuric agents should be employed. Of these Benemid appears to be the most promising yet de-

veloped. With regard to dietary restriction in gout, the situation still is unsettled. In patients subject to frequent recurrences of acute gout and in those with chronic gouty arthritis it seems prudent to restrict the purine, protein and alcoholic intake.

REFERENCES

1. Barnes, F. W., Jr. and Schoenheimer, R. *J. Biol. Chem.*, 151: 123, 1943.
2. Sonne, J. C., Buchanan, J. M. and Delluva, A. M. *J. Biol. Chem.*, 173: 69, 1948.
3. Buchanan, J. M., Sonne, J. C. and Delluva, A. M. *J. Biol. Chem.*, 173: 81, 1948.
4. Shemin, D. and Rittenberg, D. *J. Biol. Chem.*, 167: 875, 1947.
5. Karlsson, J. L. and Barker, H. A. *J. Biol. Chem.*, 177: 597, 1949.
6. Sakami, W. *J. Biol. Chem.*, 176: 995, 1948.
7. Stetten, M. R. and Fox, C. L., Jr. *J. Biol. Chem.*, 161: 333, 1945.
8. Shive, W., Ackerman, W. W., Gordon, M., Getzindaner, M. E. and Eakin, R. E. *J. Am. Chem. Soc.*, 69: 725, 1947.
9. Edson, N. L., Krebs, H. A. and Model, A. *Biochem. J.*, 30: 1380, 1936.
10. Schulman, M. P., Buchanan, J. M. and Millen, C. S. *Federation Proc.*, 9: 225, 1950.
11. Plentl, A. A. and Schoenheimer, R. *J. Biol. Chem.*, 153: 203, 1944.
12. Brown, G. B., Roll, P. M., Plentl, A. A. and Cavalieri, L. F. *J. Biol. Chem.*, 172: 469, 1948.
13. Bendich, A., Getler, H. and Brown, G. B. *J. Biol. Chem.*, 177: 565, 1949.
14. Hammarsten, E., Reichard, P. and Saluste, E. *J. Biol. Chem.*, 183: 105, 1950.
15. Hammarsten, E. and Hevesy, G. *Acta physiol. Scandinav.*, 11: 355, 1946.
16. Furst, S. S., Roll, P. M. and Brown, G. B. *J. Biol. Chem.*, 183: 25, 1950.
17. Benedict, J. D., Forsham, P. H. and Stetten, DeW., Jr. *J. Biol. Chem.*, 181: 183, 1949.
18. Benedict, J. D., Forsham, P. H., Roche, M., Soloway, S. and Stetten, DeW., Jr. *J. Clin. Investigation*, 29: 1104, 1950.
19. Cavalieri, L. F., Blair, V. E. and Brown, G. B. *J. Am. Chem. Soc.*, 70: 1240, 1948.
20. Geren, W., Bendich, A., Bodansky, O. and Brown, G. B. *J. Biol. Chem.*, 183: 21, 1950.
21. Berliner, R. W., Hilton, J. G., Yü, T. F. and Kennedy, T. J., Jr. *J. Clin. Investigation*, 29: 396, 1950.
22. Talbott, J. H. and Coombs, F. S. *J. A. M. A.*, 110: 1977, 1938.
23. Brøchner-Mortensen, K. *Acta med. Scandinav.*, 106: 81, 1941.
24. Friedman, M. and Byers, S. O. *Am. J. Med.*, 9: 31, 1950.
25. Gutman, A. B. and Yü, T. F. *Am. J. Med.*, 9: 24, 1950.
26. Wolfson, W. Q., Cohn, C., Levine, R. and Huddleston, B. *Am. J. Med.*, 4: 774, 1948.

Clinico-pathologic Conference

Pulmonary Disease with Hyperglobulinemia

STENOGRAPHIC reports, edited by Robert J. Glaser, M.D., and David E. Smith, M.D., of weekly clinico-pathologic conferences held in the Barnes Hospital, are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, A. G. (No. 174817), a white laborer fifty-two years of age, entered the Barnes Hospital on August 2nd, 1949, complaining of a cough. The family history was of interest in that the patient's father had died at the age of sixty-six of tuberculosis and one brother had died at twenty-four with "asthma and heart trouble." In regard to his past history the patient stated that he had had a cataract in the left eye since birth. He had acquired gonorrheal infections on a number of occasions and eventually developed a urethral stricture. When he was thirty-two he had a penile lesion for which he received very little treatment. At the age of 44 during an army examination he was told that he had a "4-plus Wassermann." He was given antisyphilitic therapy, consisting of intramuscular injections once weekly, and intravenous injections three times weekly for a period of three to four months. After the last intravenous injection a generalized skin eruption developed which gradually disappeared. For several years before entry he had had nocturia and frequency. His diet had been variable; periodically he consumed large amounts of whiskey and during these periods he ate poorly. He had worked in lead and zinc mines, in a foundry and in a rock quarry.

Twenty years before admission to the hospital the patient was told that he had tuberculosis of the right lung; at the time he had no symptoms and continued working in the mine in which he was employed. About eighteen months before entry the patient drank excessively for three or four days. During this period he was frequently out-of-doors, exposed to inclement, cold weather without adequate clothing, and a respiratory infection developed which was diagnosed as pneumonia. He had a fever up to 105°F. for about two weeks; his temperature then fell to 103°F. where it remained for a third week. He was given eleven injections of penicillin and an unknown amount of sulfonamides. During this illness he had a cough productive of foul yellow sputum and at times brought up as much as two cups of sputum daily. In addition he noted marked dyspnea.

He limited his physical activity until a year before entry at which time, after carrying a heavy basket for some distance, he suddenly became extremely weak and noticed a great increase in dyspnea. Dyspnea became extreme over a period of three months, and the patient consulted a physician who performed a thoracentesis. Five quarts of brownish fluid were removed from the right side of his chest; the procedure brought prompt relief of dyspnea. The patient did not complain of fever or chills at this time, but he continued to cough and occasionally noticed blood in sputum. Five months prior to entry his cough became intense and hemoptysis was persistent; he produced as much as a cupful of blood on a single occasion. Four months before admission his abdomen began to swell. Two months later he noticed nausea, vomiting and increased cough. He again consulted a physician who removed about three quarts of brownish fluid from his abdomen. X-ray films were taken and the patient was told that "something on the left side was pushing his intestines to the

right." Soon thereafter he experienced several attacks of knife-like pain to the right of the sternum; the pain extended through to the back and was aggravated by respiration. The patient was admitted to the State Cancer Hospital where he was told that no evidence of cancer or of lung abscess was obtained, and he was advised to come to the Barnes Hospital for further study.

Physical examination at the time of entry revealed the patient's temperature to be 37.3°C., pulse 108, respiration 24, blood pressure 95/65. The patient was a thin, poorly nourished, pale, chronically ill man, who coughed frequently and produced considerable amounts of mucopurulent sputum. The fingers were definitely clubbed. His vision was markedly impaired on the left where a cataract was noted. The pupils were unequal and reacted only slightly to light and accommodation. The right fundus appeared normal. The teeth were carious. A few small cervical lymph nodes were palpable. Examination of the chest revealed that expansion was limited; there was dullness to percussion and absent breath and voice sounds over the lower two-thirds of the right lung posteriorly. A few rales were heard above this area and a few crepitant rales were heard at either apex. Examination of the heart revealed no abnormalities. The abdomen was slightly protuberant and shifting dullness was elicited but no organs or masses were felt. Bilateral indirect inguinal hernias were present. Rectal examination revealed marked enlargement of the prostate. Neurologic examination was not remarkable.

The laboratory data were as follows: Blood count: red cells, 2,880,000; hemoglobin, 6.75 gm.; white cells, 6,000; differential count: eosinophils 2 per cent; stab forms 2 per cent; segmented forms 66 per cent; lymphocytes 27 per cent; monocytes 3 per cent. Urinalysis: entirely negative, including examination for Bence-Jones protein. Stool examination: guaiac negative. Blood Kahn test: positive. Cardiolipin test: positive in undiluted specimen. Blood chemistry: non-protein nitrogen, 26 mg. per cent; total proteins, 10.7 gm. per cent; albumin, 2.6 gm. per cent; globulin, 8.1 gm. per cent; thymol turbidity test, 9.3 units; cephalin-cholesterol flocculation test, 1 plus; van den Bergh's test, within normal limits. Sputum culture: alpha and beta hemolytic streptococci. Sputum smear: no acid-fast bacilli seen. Venous pressure: 95 mm. saline. Circulation time (decholin): eighteen seconds. Vital capacity: 2.1 L. Basal metabolic rate: plus 18 per cent. Roentgenogram of the chest (Fig. 1): "There is marked deviation of the trachea and mediastinum to the right, atelectasis of the right middle and right lower lobes and emphysema of the upper lobe. Both hilar regions show calcification of the "egg shell" type. There is questionable pneumoconiosis. A pleural effusion is noted at the right base." Sinus films: Thickening of the mucous membranes of the left maxillary antrum. Skull films: negative. Flat film of the abdomen: findings suggestive of ascites. Intravenous pyelograms: "There is incomplete filling of the calices of the left kidney and some dilatation of the inferior calix on that side." Electrocardiogram: within normal limits.

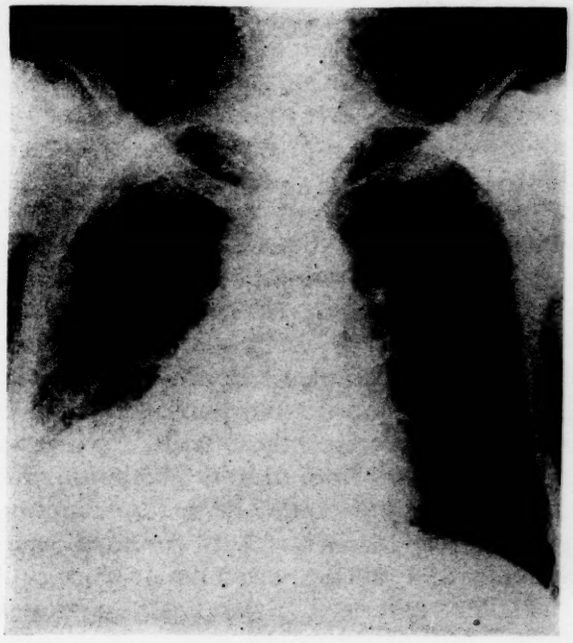


FIG. 1. A film of the chest showing mediastinal shift to the right, hilar calcification and right pleural effusion.

Shortly after the patient was admitted a thoracentesis was performed on the right and 30 cc. of clear yellow fluid were withdrawn. No cells were seen on microscopic examination. The protein content of the fluid was 6.9 gm. per cent and smears were negative for acid-fast organisms. A first strength purified protein derivative test was negative but the second strength was positive. Many subsequent sputum examinations for tubercle bacilli were negative. Sternal bone marrow aspiration revealed groups of plasma cells in some areas which appeared more like those seen in chronic infection than in multiple myeloma. No definite diagnosis could be made from the preparation. Bronchograms revealed non-visualization of the bronchial radicles of the right middle lobe and of the major bronchial radicle of the right lower lobe. There was bronchiectasis of the right lower lobe.

The patient was transferred to the Chest Surgical Service where bronchoscopy was performed. The left bronchial tree was found to be normal; on the right there was narrowing of the lumens of the middle and lower lobe bronchi with granulations which bled easily. A sputum preparation was questionably positive for carcinoma cells. Biopsy taken from a bronchus revealed only chronic inflammation. Three other sputum examinations for carcinoma cells were negative. It was decided to perform an exploratory thoracotomy in order to make a definite diagnosis.

At the time of operation the right lung was found to be densely bound to the chest wall and the normal anatomic relationships were obscure. A firm mass was present in the hilus. The right lower and middle lobes were firm and atelectatic. A pneumonectomy was attempted but during the procedure the pulmonary vein was inadvertently torn; severe hemorrhage occurred which was controlled with difficulty. The lung was finally resected, but during the procedure the tear in the pulmonary vein extended into the right auricle and uncontrollable bleeding resulted. The patient expired on August 25, 1949.

DISCUSSION

DR. HARRY L. ALEXANDER: This patient had several pulmonary diseases. We shall attempt first to evaluate each of them and, second, to see if they can be fitted into a single total picture. The history indicates that the patient's father died of tuberculosis, and twenty years before the patient came to the hospital, when he was thirty-two, he was told that he had tuberculosis of the right lung. Apparently he was not ill for he continued to work as a miner. At various times he worked in lead and zinc mines, then in a foundry and later in a rock quarry. Dr. Goldman, will you discuss the industrial hazards to which this patient was exposed?

DR. ALFRED GOLDMAN: In both lead and zinc mines as well as in rock quarries workers are exposed to free silica. Lead and zinc mines in certain areas of Missouri are notorious for the hazard of silicosis which they present to those who work in them. The "egg shell" calcification which was noted on this man's chest x-ray constitutes evidence of silicosis since no other lesion produces quite the same picture, particularly in the hilar region. Calcification may be secondary to superimposed tuberculosis or it may occur in silicotic nodules. I am sure that this patient had pneumoconiosis.

DR. ALEXANDER: Would you comment on the relation between silicosis and pulmonary tuberculosis?

DR. GOLDMAN: Silicosis certainly predisposes to pulmonary tuberculosis; indeed, pulmonary tuberculosis develops in the majority of patients with silicosis.

DR. ALEXANDER: About eighteen months before entry the patient had an episode which was diagnosed as pneumonia; subsequently he was troubled with a chronic cough and excessive sputum production. Do you believe that he had chronic bronchitis?

DR. GOLDMAN: He probably had both bronchitis as well as bronchiectasis.

DR. ALEXANDER: About a year before entry while carrying a heavy load the pa-

tient suddenly became weak and quite dyspneic. Dr. Smith, will you explain the sudden dyspnea?

DR. JOHN R. SMITH: The fact that his dyspnea came on suddenly while he was carrying a heavy load suggests to me the possibility of circulatory embarrassment. On the other hand, subsequent studies here indicated that the heart was much less involved than the lungs. One would therefore probably have to explain the sudden dyspnea on the basis of pulmonary disease.

DR. ALEXANDER: Dr. Wilson, do you believe the chest x-ray indicates cardiac enlargement?

DR. HUGH M. WILSON: I think probably there was left ventricular hypertrophy.

DR. ALEXANDER: This man did not have hypertension. Why should he have had an enlarged left ventricle, Dr. Smith?

DR. SMITH: I do not know.

DR. ALEXANDER: Dr. Flance, the radiologists also suggested the diagnosis of emphysema in this man. If a patient has a vigorous daily cough for eighteen months, do you believe that emphysema would be likely to develop?

DR. I. JEROMOE FLANCE: A man might cough for eighteen months without developing emphysema. The answer to the question depends upon the degree of obstruction. If there is bronchial obstruction, obstructive emphysema may well result. On the other hand, if there is no obstruction, a patient may cough severely over several years without obvious emphysema developing.

DR. ALEXANDER: I am inclined to disagree with you on this point, Dr. Flance. We studied this problem some years ago and concluded that emphysema was apt to develop if a patient coughed with vigor repeatedly over a long period of time.

Before we consider other points, Dr. Goldman, may we dismiss syphilis of the lung as a possibility? This man had a weakly positive serologic test for syphilis.

DR. GOLDMAN: I think we may. It is extremely rare.

DR. ALEXANDER: This patient had an increased number of plasma cells in the bone marrow and an inverted albumin-globulin ratio. It was said that the plasma cells resembled more those of chronic infection than of multiple myeloma. Dr. Wiegand, how does a hematologist make this differentiation?

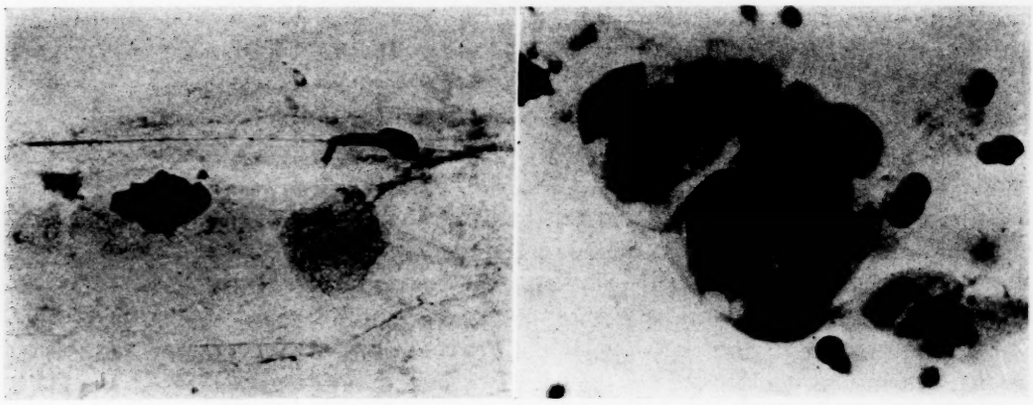
DR. HERBERT C. WIEGAND: In chronic infection the plasma cells have a normal appearance with the typical eccentrically placed, small, pyknotic nucleus; in multiple myeloma the abnormal tumor cells are larger, have a considerably larger nucleus, a much finer chromatin network, and nucleoli are often seen.

DR. ALEXANDER: Dr. Taussig, would you comment on the hyperglobulinemia?

DR. BARRETT L. TAUSSIG: The globulin value recorded here is higher than any I remember. An elevated globulin is frequently recorded in long-standing pyogenic infections. Certain other diseases, for example kala-azar, sarcoid and cirrhosis, may also be associated with an elevated globulin.

DR. ALEXANDER: A sputum specimen from this patient was examined in the surgical pathology laboratory and was questionably positive for carcinoma cells. Exfoliative cytology is finding wide application as a diagnostic procedure and I should like to ask Dr. Ackermann to comment on his findings in this case and on this method in general.

DR. LAUREN V. ACKERMANN: May I first correct the protocol and say that one sputum specimen was reported as "suspicious" and three others were negative. The finding of "suspicious" cells does not necessarily mean they are cancer cells but does indicate that further specimens are required. In the first eleven months that sputa and bronchial washings were examined for cancer cells specimens from 270 patients were submitted; in 100 instances the patients were proved to have bronchiogenic carcinoma. Sputa from sixty-one of these 100 patients were reported as positive for cancer cells; in twenty-five of the 100 patients the lesion was resectable. In one instance a false positive was reported in a patient with



2 3

FIG. 2. A group of malignant cells with prominent nuclei and nucleoli.
FIG. 3. Atypical cells occurring in a patient who had squamous metaplasia of the bronchi. These cells closely simulate those of carcinoma.

lipoid pneumonia. Sixteen (64 per cent) of the twenty-five patients with resectable tumors showed cancer cells in their sputa. Of these same twenty-five cases there were only nine (36 per cent) in which a positive bronchoscopic biopsy was obtained. This finding emphasizes the fact that in resectable early bronchiogenic carcinoma a positive bronchoscopic biopsy is obtained in only 30 to 40 per cent of instances. In six instances before exploratory thoracotomy the cytologic diagnosis was the only positive microscopic evidence of cancer. In two of the six it was possible to substantiate the presence of cancer by examination of a frozen section, but in the remaining four resection was based solely on the cytologic diagnosis of cancer.

We report our specimens in four ways: insufficient, negative, suspicious (this interpretation may be applied to specimens from patients with many diseases and does not therefore necessarily mean bronchiogenic carcinoma is present) and positive. The diagnosis of cancer depends mainly on nuclear changes in the cells. There is an increase in the size of the nucleus at the expense of the cytoplasm, and nucleoli become prominent. (Fig. 2.) At times clusters of cancer cells occur which we believe are absolutely diagnostic. There is another group of cases in which errors can be made. Bizarre cells appear in squamous metaplasia (Fig. 3) and macrophages are difficult to differentiate from carcinomatous cells. Such cells appear quite frequently when there is chronic inflammation of the lung; thus they may be seen in such diverse conditions as tuberculosis, organizing pneumonia, chronic lung abscess, lipoid pneumonia and bronchiectasis. This test therefore has certain limitations. If one knows its limitations, he can use it as a valuable adjunct in making the diagnosis of bronchiogenic carcinoma.

In summary, examination of sputa and bronchial aspirations may be positive in a relatively high percentage of resectable cancers of the lung. This percentage can rise to approximately 85 per cent providing adequate specimens are submitted, multiple specimens are examined (three to five) and, most important, the pathologist examining the specimens is well trained in this technic. With added experience the percentage of false positives should be reduced to a very low level (1 per cent).

DR. ALEXANDER: Thank you very much, Dr. Ackermann. Dr. Wood, on the basis of Dr. Ackermann's comments, would you make a diagnosis of carcinoma in this case?

DR. W. BARRY WOOD, JR.: No, I would not.

DR. ALEXANDER: How do you feel about this point, Dr. Goldman?

DR. GOLDMAN: Carcinoma of the bronchus must be considered when a patient has atelectasis. On the other hand, broncho-

scopy did not show a tumor where one would have expected to find it in view of the fact that there was atelectasis of two major lobes.

DR. ALEXANDER: Would you consider it unusual in regard to carcinoma that a thoracentesis was performed on admission but no more fluid had to be removed subsequently?

DR. GOLDMAN: I believe that fact is against the diagnosis of a malignant effusion. Usually when pleural effusion occurs because of metastatic tumor it continues to recur after thoracentesis.

DR. ALEXANDER: How often is ascites seen in bronchogenic carcinoma?

DR. GOLDMAN: Ochsner found the incidence of ascites to be 4.8 per cent in 3,000 cases of lung cancer.

DR. ALEXANDER: In one series which I reviewed ascites was not encountered in 356 patients with bronchogenic carcinoma.

DR. AXEL R. GRONAU: I would not be willing to dismiss the possibility of carcinoma lightly. Silicosis may be associated with carcinoma of the lung. In the series of Schneeberg miners studied in Germany the coexistence of carcinoma and silicosis was surprisingly high.

DR. GOLDMAN: In my experience carcinoma is not particularly common in silicotics.

DR. ACKERMANN: May I add a remark about the series of cases in Germany to which Dr. Gronau referred? There were two groups of patients. In one group silicosis existed, whereas in the other group there was no silicosis. The frequency of bronchogenic carcinoma was high in both groups, but it was thought that the common denominator in both groups was their exposure to radioactive material.

DR. ALEXANDER: This patient had a family history and a past history of tuberculosis. Further, he coughed up blood. Dr. Flance would you care to defend the diagnosis of tuberculosis?

DR. FLANCE: This patient had an alcoholic history, hepatomegaly by x-ray, and hyperglobulinemia. We have done routine serum protein determinations on our admissions to the Koch Hospital for the last ten or twelve years but have never seen such a high globulin in a patient with uncomplicated tuberculosis. I think one might postulate that the patient also had cirrhosis. It is well known that tuberculosis is prone to develop in cirrhotics; they probably are more susceptible to the disease than are non-cirrhotics. Whether this susceptibility is environmental or due to some defect in their immune mechanism is impossible to say. In their review of cirrhosis Patek and Ratnoff found that tuberculous peritonitis developed in 10 per cent of their patients. Our incidence is not that high but certainly tuberculous peritonitis must be considered here as an explanation for the ascites. To explain the pulmonary findings on a tuberculous basis, however, is difficult because the findings were not particularly suggestive of pulmonary tuberculosis unless there was tuberculous endobronchitis with granulation and narrowing of the lumen and subsequently obstruction and secondary infection behind.

DR. ALEXANDER: Except for the hyperglobulinemia the liver function tests were essentially normal. I would think, therefore, that it would be difficult to make a diagnosis of cirrhosis in this patient.

DR. CARL G. HARFORD: It was stated in the protocol that numerous acid-fast stains were negative for acid-fast bacilli. It should be pointed out that that method for detecting tubercle bacilli is a very crude one. On checking back in the laboratory I discovered that several guinea pigs were inoculated with sputum from this patient, but unfortunately the animals died of an unrelated cause before an adequate time had elapsed for the development of tuberculous lesions. It would seem likely that a patient with as much silicosis as this man exhibited would also be a very good candidate for tuberculosis.

DR. ALEXANDER: How do you interpret the tuberculin test?

DR. HARFORD: The results of the tuberculin test do not help one way or the other

since many patients without active tuberculosis have positive skin tests.

DR. ALEXANDER: This man had involvement of the lower lobe without evidence of infection in the upper lobe. Dr. Flance, is that not somewhat unusual in tuberculosis?

DR. FLANCE: In adults, of course, the upper lobes are more commonly involved by tuberculosis. A few years ago, however, we reviewed our cases and found an incidence of 3 per cent of lower lobe tuberculosis of the reinfection type. Such involvement is particularly common in patients who are most susceptible to the disease, especially those with diabetes, cirrhosis or with decreased resistance from whatever cause.

DR. GOLDMAN: I think tuberculosis is probably the most likely diagnosis, but to explain it, as Dr. Flance has pointed out, one would have to assume that the patient had tuberculous bronchitis with stenosis and bronchiectasis.

DR. WOOD: I should like to ask about the history of the acute episode of pneumonia. Patients with bacterial pneumonia do not as a rule have a three-week course with high temperature unless there is a complication, and the most likely complication is empyema. Therefore, I believe that the entire process which this patient had possibly could be explained on a pyogenic basis, beginning with acute bacterial pneumonia, complicated by empyema which became chronic and loculated. The fact that only 30 cc. of fluid were recovered on the last thoracentesis can be explained by the fact that most of the fluid present was pocketed. If the patient had empyema, it is probable that the pericardium was also involved with pericarditis.

DR. HAROLD SCHEFF: Would not the fact that the venous pressure was normal be against the diagnosis of pericarditis?

DR. WOOD: That depends on how much pericardial effusion or pericarditis is present.

DR. ALEXANDER: I think we cannot reach a definitive diagnosis in this case. Certainly carcinoma, tuberculosis and acute bacterial pneumonia with subsequent empyema must be considered. We shall have to turn to the pathologist for the correct diagnosis.

Clinical Diagnoses: ? Bronchiogenic carcinoma. ? Pulmonary tuberculosis and tuberculous peritonitis. ? Bacterial pneumonia with empyema.

PATHOLOGIC DISCUSSION

DR. JAMES C. HAWKINS: The right pleural cavity contained 350 cc. of bloody fluid. The right lung had been removed except for a collar of firm greyish tissue about the hilus that contained several enlarged lymph nodes. These nodes were firm and generally fibrous with foci of calcification surrounded by black pigment. In one there was a focus of caseous necrosis. The pleural surface of the right leaf of the diaphragm was covered by a layer of soft, spongy fibrin 5 mm. thick in which there were fine pockets of loculated, thick fluid. Numerous firm fibrous nodules 5 mm. or less in diameter were present throughout the left lung and there were several calcified nodules of equal size in each lobe. In the parenchyma several poorly delimited irregular foci of firm grey tissue up to 5 cm. in greatest diameter had the gross appearance of organized pneumonia. The lingula of the left lung was atelectatic and its bronchi were dilated. The bronchial and tracheobronchial lymph nodes were enlarged and similar to those at the hilum of the right lung. Numerous fibrous adhesions spanned the left pleural cavity, but the serous membranes showed no gross pathologic change. The heart, pericardium and aorta were remarkable principally for the presence of moderate arteriosclerosis, more advanced in the ascending aorta; slight hypertrophy of the myocardium; and foci of fibrosis in the myocardium, one of which was 2 by 3 cm. and had the appearance of a healed infarct in the inferior part of the septum.

All the serous surfaces in the abdomen were densely studded with firm, white nodules 1 mm. in diameter, and 50 cc. of clear yellow fluid were recovered from the peritoneal cavity. Fine fibrinous adhesions

bound the loops of the intestines to one another and to the parietal peritoneum. The lymph nodes about the porta hepatis, pancreas and aorta were enlarged and contained calcified and fibrocaseous foci as well as grossly visible black pigment. The liver was enlarged, weighing 2,030 gm., and the cut surfaces had the prominent markings of congestion. The spleen weighed 400 gm. and was dark red, soft and semi-fluid. Incidental lesions in various organs included nodular hyperplasia of the prostate, a chronic abscess in the anterior lobe of the prostate, diverticula in the urinary bladder and two small traction diverticula in the esophagus over calcified tracheobronchial lymph node .

DR. ROBERT A. MOORE: Most of the problems concerning the clinical diagnosis in this case were solved by gross examination of the viscera. The small nodules over all surfaces in the peritoneal cavity and the fibrinous peritoneal adhesions were highly characteristic of tuberculous peritonitis. No evidence of carcinoma was apparent during the examination of the thoracic viscera at autopsy, nor was any found in the microscopic sections. The specimen of the surgically removed right lung was examined in Dr. Ackermann's laboratory, and he described lesions similar to but much more advanced than those in the left lung. These consisted essentially of bronchiectasis, atelectasis and organized pneumonia with the coincident presence of sharply encapsulated caseous, fibrous and calcified nodules throughout the lungs and lymph nodes. There was no evidence of caseous pneumonia, cavitation or bronchiogenic tubercules and consequently no evidence of recent active spread of the pulmonary tuberculosis or an open lesion that might have been expected to result in acid-fast bacilli in the sputum. The gross appearance was not at all suggestive of silicosis. Microscopically, some of the small fibrous nodules had the densely collagenous, whorled, almost acellular structure typical of silicosis, but their isolated occurrence and the absence of associated destructive fibrosis of the lung indicated they did not cause a clinically important disease.

Figure 4 is a photomicrograph of a section from a tracheobronchial lymph node on the side of the removed lung. Well formed tubercules with epithelioid and giant cells indicated an activity of the disease in those nodes that was considerably greater than was present in any lesion in the lungs. On the other hand, attempts to stain acid-fast bacilli in these nodes as well as in the lung were unsuccessful, although the lesions are histologically the typical granulomatous lesions of tuberculosis.

Two views of a section of the right leaf of the diaphragm are represented in Figures 5 and 6. The pleural surface is on the left side of the photographs, and at low magnification it can be seen that almost half the breadth of the section was composed of a tremendous mass of fibrinous and caseous material that formed the loculated pleurisy at that site. The more detailed view of the region just beneath the fibrinocaseous layer shows typical tuberculous granulation tissue. Acid-fast bacilli were stained in these sections. The same type of active histologic lesion formed the nodules scattered throughout the peritoneal surfaces as is illustrated in Figure 7.

In Figure 8 there is the edge of one of the encapsulated fibrocaseous nodules in a portahepatic lymph node. Active granulomatous lesions were present in these nodes as well as the inactive form illustrated. In the cytoplasm of macrophages on the right side of this photograph as well as throughout the microscopic section there was a small amount of black pigment as had been noted grossly. This anthracotic pigment was evidence of retrograde flow of lymph from the thorax which probably occurred after the tuberculosis had affected the mediastinal nodes; it was not transported to these nodes by way of the blood stream because there was no similar pigment in the spleen. Such retrograde lymphatic flow along channels through the hiatus of the diaphragm is one of the recognized manners by which pigment as well as bacilli may be transmitted

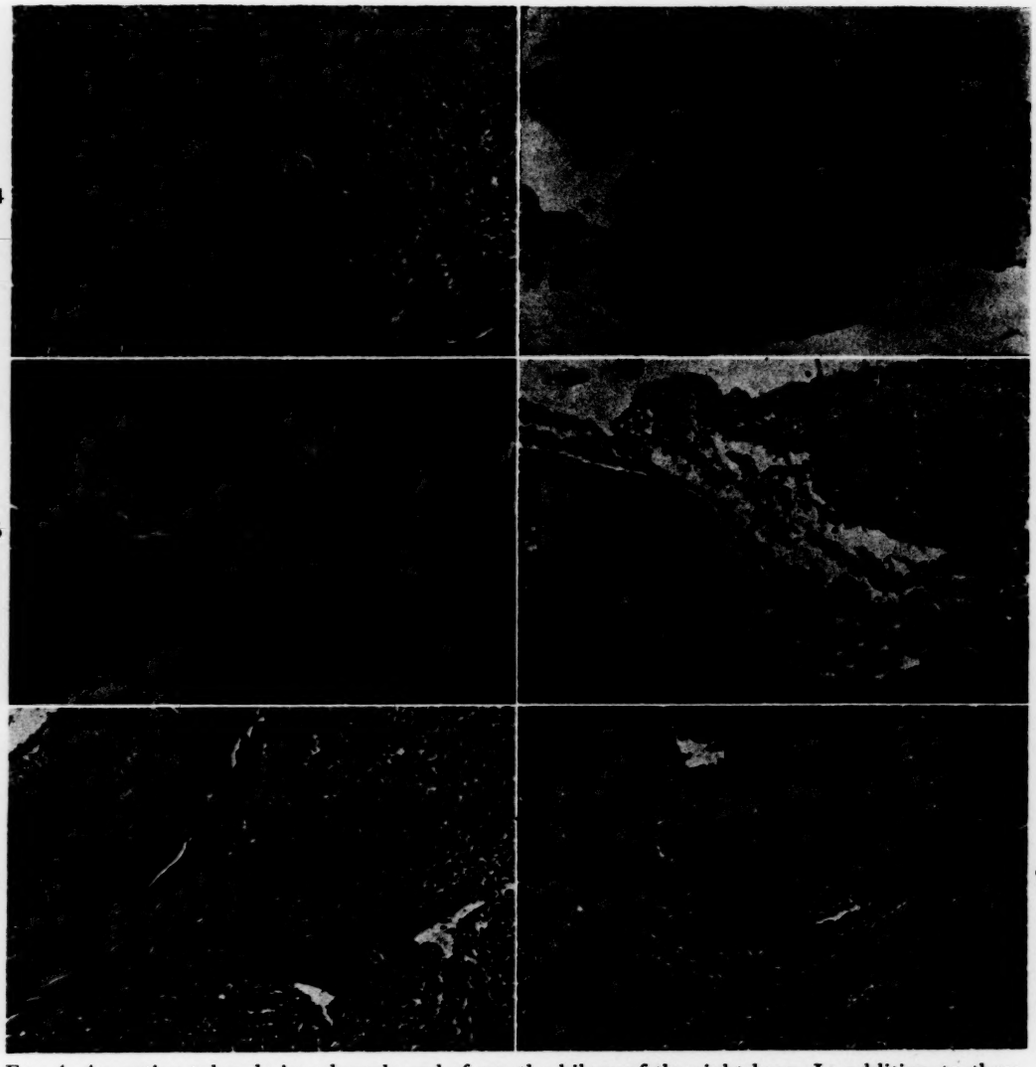


FIG. 4. An active tubercle in a lymph node from the hilum of the right lung. In addition to these lesions there were many fibrotic or calcified inactive nodules in these nodes as well as in the lungs.
FIG. 5. Loculated tuberculous pleurisy on the right leaf of the diaphragm. Almost the entire left half of the section is composed of caseous and fibrinous exudate.
FIG. 6. Active tuberculous granulation tissue in the middle zone of the section in Figure 4. Acid-fast bacilli were stained in these lesions.
FIG. 7. Nodules of tuberculous peritonitis from the serosal surface of a section of ileum.
FIG. 8. An encapsulated, fibrotic nodule in a lymph node of the porta hepatis. Anthracotic pigment in these nodes without similar pigment in the spleen indicated that tubercle bacilli responsible for these inactive lesions, as well as other active ones, passed through the diaphragm by way of lymphatic channels.
FIG. 9. A small epithelioid tubercle in the spleen. Small recent lesions such as those in the liver and spleen indicated a terminal vascular dissemination of tubercle bacilli.

through the diaphragm and explains the pathogenesis of the abdominal lymph node tuberculosis in this case. Rupture of a lesion in one of these nodes with release of organisms into the peritoneal cavity was probably the method by which the peritoneum was infected although there was a terminal vascular dissemination of the disease. This latter feature is illustrated by the small, recent epithelioid tubercule in the spleen shown in Figure 9. There were a few similar recent lesions in the liver, but their character, size and number indicated they were not an important event in the observed clinical course of this patient.

An evaluation of the various lesions indi-

cative of this patient's diseases and points considered in the differential diagnosis would rate silicosis as present but probably not clinically important. Tuberculosis was present in the lungs but was of only slight significance as the lesions were encapsulated and inactive; in the peritoneum tuberculosis was of major clinical importance. There was no pericarditis. We were not impressed with any emphysema, either grossly or microscopically; the recognition of that lesion, however, is largely a matter of judgment in inspection of the fresh gross specimen and a small degree of emphysema can easily go undetected. The dominant disease of the lungs was chronic bronchitis, bronchiectasis and organized pneumonia; all were due to a chronic infection that was not tuberculosis. It was our interpretation that the appearances and stages of these lesions could be best correlated with the episode of pneumonia recounted in the patient's history, and that from that event there were progressive complications of organization, bronchiectasis, chronic bronchitis and severe compromise of the respiratory function. The exact cause of the onset of the tuberculous peritonitis or its relationship to the chronic inflammation in the lungs was not obvious, although from the history and histologic appearance of the lesions it probably began about four months before the patient's death and resulted in terminal miliary tuberculosis which undoubtedly would have eventually caused death had it had time to progress.

Final Anatomic Diagnoses: Tuberculosis and bronchiectasis of the middle and lower lobes of the right lung with healed, partially healed and recent foci at the hilum; calcified and fibrous nodules in both lobes of the left lung; calcified and fibrocaseous nodules in the peribronchial tissues and the bronchopulmonary, tracheobronchial, mediastinal, periaortic and portahepatic lymph nodes; miliary tuberculosis of the liver and spleen, slight; tuberculous peritonitis.

Acknowledgment: Illustrations were made by the Department of Illustration, Washington University School of Medicine.

Case Report

Thrombocytopenic Purpura Due to Allergy to Quinidine*

Study of the Mechanism of Thrombocytopenia

ERWIN O. HIRSCH, M.D. *and* WILLIAM DAMESHEK, M.D.

Boston, Massachusetts

THROMBOCYTOPENIC purpura indistinguishable from true idiopathic thrombocytopenic purpura may be a manifestation of allergy. Among the agents described as causative factors the organic arsenicals and sedormid (allyl-isopropyl-acetyl-carbamide) have been most frequently implicated. Many other drugs and even foods have been held responsible in isolated instances. Among these quinine has been reported several times[1,2] and four reports deal with single cases of thrombocytopenia due to quinidine.[3–6]

The subject of this report is another instance of thrombocytopenic purpura at first thought to be "idiopathic." Quinidine was suspected as the causative agent after a thorough investigation into the drug intake of the patient was made. This suspicion was confirmed when the patient reacted to intentional re-exposure to this drug with another episode of severe thrombocytopenia. Observations on the patient's prothrombin consumption[7] and a consideration of the mechanism of thrombocytopenia are also included.

CASE REPORT

U. B., a fifty-eight year old white married housewife, was admitted to the New England Center Hospital on May 25, 1949, with the chief complaint of purpura of six days' duration. In December, 1948, she consulted a physician because of occasional attacks of palpitation during the past year. Quinidine sulfate (0.2 gm.) four times daily was prescribed and taken regularly for about a month. On April 14, 1949, she experienced another attack of palpitation and again took quinidine in the same dosage. One week later she suddenly developed a chill followed with a feverish sensation which subsided in less than half an hour. As the sensation of heat subsided, she noticed blood oozing from the gums; and within a few hours pinpoint bright red, purpuric lesions developed all over the body. Within the next day or two many large black and blue marks developed without relation to trauma and the patient was admitted to a community hospital.

Within two days bleeding from the gums ceased, purpura disappeared and no new ecchymoses developed. Treatment with vitamin K and iron was begun in the hospital and was continued for several weeks after discharge. The remaining ecchymoses gradually cleared and the patient was free of any hemorrhagic symptoms until May 19, 1949, when toward evening chills and fever again developed followed with bleeding from the gums, purpura and ecchymoses. These symptoms developed after the patient had taken four doses of quinidine because of an attack of palpitation which had occurred the same evening. This was the first time the patient had taken quinidine since just before her first attack of purpura. She was again taken to the hospital. Throughout her hospital stay she took 0.2 gm. of quinidine sulfate four times daily. Although the first attack of purpura had cleared in two days, this attack became increasingly severe and bleeding from the gums continued.

The legs and trunk became covered with confluent petechiae and a few appeared on the face and arms and over pressure points of the

* From the Ziskind Research Laboratories (Hematology) of the J. H. Pratt and New England Centre Hospitals, and the Department of Medicine, Tufts College Medical School, Boston, Mass. Aided by grants from the C. H. Hood Foundation and Merck & Co.

back. Large ecchymoses developed over all parts of the body and new petechiae and ecchymoses appeared daily. Two days before the patient left the hospital a weeping rash developed around her mouth; this became the site of extensive purpura and small local hemorrhages. Because of the persistence of purpura she was referred to our care.

Although the patient had always bruised easily in the past, this had never been severe or spontaneous. She had never previously had petechiae, bleeding from the gums or excessive bleeding from minor cuts or after dental extractions. There had never been any menorrhagia or nosebleeds. Except for the attacks of palpitation already mentioned and a moderate elevation of the blood pressure known for several years, her general health had always been excellent. There was no bleeding tendency in members of her family.

On examination the most striking finding was a generalized hemorrhagic eruption. The patient's skin was covered with innumerable petechiae both discrete and confluent, varying in color from bright red to dark purple. Around the mouth there was a crusting rash, the site of heavy infiltration of blood. There were many large ecchymoses. Several small blood blisters were present on the mucous membranes of the mouth and tongue. There was no active bleeding from the gums or the nose and no hemorrhages in the ocular fundi. Despite the extensive skin reaction the patient felt strong and active. There was no jaundice or lymphadenopathy. The liver and spleen were not palpable. Examination of the heart and lungs was negative. There was no bleeding from the vagina or rectum and there was no edema. Neurologic examination revealed no abnormal findings. The oral temperature was 99.2°F. and the pulse rate 68 with normal sinus rhythm. The blood pressure was 170 mm. Hg systolic and 90 diastolic.

X-rays of the chest and abdomen revealed no abnormal findings. The liver and spleen did not appear enlarged. An electrocardiogram was within normal limits and showed the presence of normal sinus rhythm and no extrasystoles. The urine was negative. No red cells were seen in the sediment. The stools were positive for occult blood. The sedimentation rate (Westergren) was 16 mm. in one hour.

Blood studies revealed the following: hemoglobin 13.7 gm. (88 per cent), red blood cells, 4.76 million, white blood cells 15,100, polymorphonuclears 71 per cent (band forms 11 per cent, lymphocytes 21 per cent, monocytes 6 per cent and eosinophiles 2 per cent). The red and white cells appeared normal but only a rare platelet was seen. The platelet count (Dameshek's indirect wet smear technic) was 32,080 (normal 400,000 to 600,000). The bleeding time (Duke) was greater than ten minutes, at which time bleeding was stopped by pressure. The tourniquet test was markedly positive. There was only minimal clot retraction after six hours. Clotting time (Lee-White) was ten minutes in the first tube and fourteen and fifteen minutes in the second and third tubes, respectively. Prothrombin time (Quick) was twelve seconds. Prothrombin time of serum was six seconds fifteen minutes after clotting, 16.5 seconds one hour after clotting, and twenty-seven seconds four hours after clotting (diminished prothrombin consumption).

FIG. 1. A megakaryocyte as seen in the bone marrow smear at the height of the intentionally produced reaction.

Bone marrow aspiration yielded a normocellular preparation in which there was a normal ratio of myeloid to erythroid elements. There was normal progression of maturation, no eosinophilia and no evidence of a leukemic or other infiltrative process. Megakaryocytes were present in normal numbers but showed perfectly smooth, round, cytoplasmic outlines without the usual scalloping and lacunae along their margins, and appeared to be devoid of platelet production. (Fig. 1.)

No treatment was given but quinidine was discontinued as soon as the patient entered the hospital. Beginning twelve hours after entry no fresh petechiae or ecchymoses were noted. All skin lesions including the rash around the mouth

cleared within a week. There was no recurrence of bleeding from the gums and no new bleeding from any site. The platelet count rose to normal levels during the first week after admission. The course of the platelet count is shown in Figure 2.

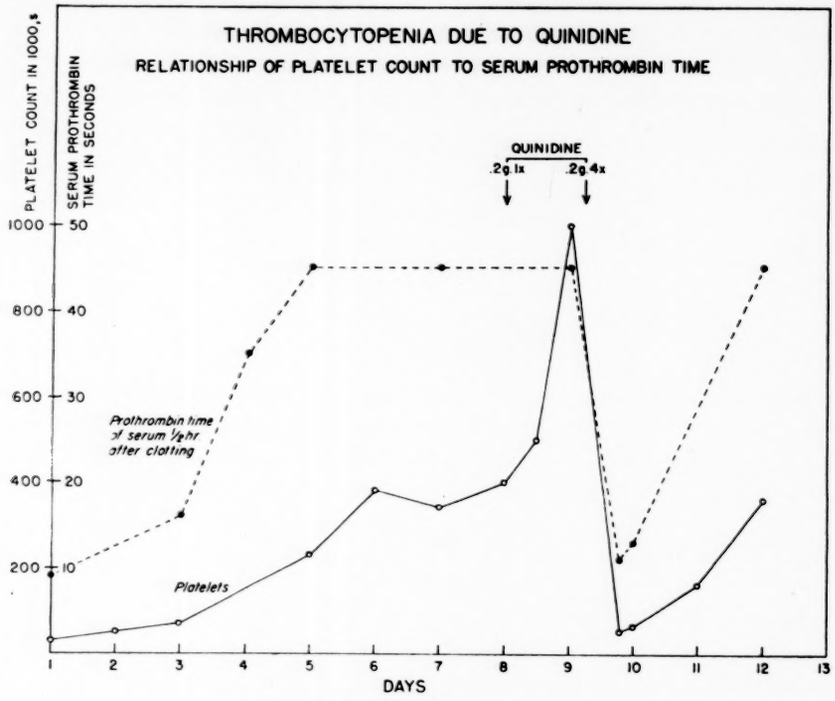


FIG. 2.

On the morning of the eighth hospital day the patient was given a test dose of 0.2 gm. of quinidine sulfate by mouth. Throughout this day she complained of slight generalized itching but there were no hemorrhagic phenomena. Platelet counts done eight and twenty-four hours later revealed a further rise in the number of platelets to one million (twice normal) and all itching had ceased. She was now given four doses of 0.2 gm. quinidine sulfate at intervals of four hours. Shortly after the second dose had been given the patient again complained of generalized itching. This persisted until the drug was omitted. Fourteen hours after the first dose the patient noticed oozing of blood from the gums and a few petechiae appeared over pressure areas. A platelet count at this time was 47,040 per cu. mm. The bleeding time was markedly prolonged and a tourniquet test was strongly positive. Clot retraction was absent. Clotting time and plasma prothrombin time were normal. The serum prothrombin time was three seconds fifteen minutes after clotting, and ten seconds one hour after clotting. A bone marrow puncture revealed a preparation identical in appearance with that obtained on admission. The hemorrhagic phenomena subsided within twenty-four hours. The platelet count began to rise two days later and reached practically normal values by the fourth day. Sixty hours after the reaction, when the platelet count was still only about one-third of normal, examination of the sternal marrow revealed the megakaryocytes to be entirely normal. The cytoplasmic outlines were now marked by much scalloping and large masses of platelets were seen to lie in the lacunae. (Fig. 3.)

COMMENTS

The Mechanism of the Thrombocytopenia. In their study of the megakaryocytes in idiopathic thrombocytopenic purpura Dameshek and Miller[8] emphasized that the finding of at least normal numbers of megakaryocytes in the bone marrow together with a great diminution of platelet production by these cells was the most important diagnostic feature serving to differentiate idiopathic thrombocytopenic purpura from other thrombocytopenic states. The lack of a marrow destructive process and of any evidence to suggest a fundamental disease causing splenomegaly were corollary findings.

The case described in this paper showed findings identical with those seen in the idiopathic group. Although in most cases of this disease the etiology is actually unknown, in this case quinidine was shown to be the causative agent. Since at first the patient had taken this drug without any ill effects although on three subsequent occasions purpura developed whenever she took it for a sufficient length of time, it seems clear that the mechanism of the thrombocytopenia was one of hypersensitivity to quinidine. The appearance of the megakaryocytes suggest that this was due in some measure to inhibitory effects upon the platelet production from the megakaryocytes.

The most dramatic feature in this case was the quick drop in platelet count from one million per cu. mm. to approximately 50,000 within fourteen hours following the administration of a sufficient amount of quinidine. Isolated experiments during the last forty years have led to the conclusion that the life span of the platelet is between two and seven days,[9–11] The virtual disappearance of the platelets within fourteen hours after administration of the drug can thus not be accounted for by inhibition of platelet formation alone. Instead it is clear that the thrombocytopenia was due at least in part to destruction of the platelets in the circulation. Because there were no indications of platelet thromboses, it is unlikely that the platelets had been merely diverted from the active circulation.

In Nudelman's case[4] the platelets disappeared from the blood six hours after a test dose of quinidine. Comparable data are not available in the three other cases of thrombocytopenia due to quinidine hypersensitivity which are reported in the literature. Moeschlin[12] in his study of thrombocytopenic purpura due to sedormid pointed out that purpura occurred only after previous sensitization to the drug, that the drop in platelet count occurred about one hour after ingestion of the drug and that the bone marrow contained normal numbers of megakaryocytes. Although he made no note of platelet

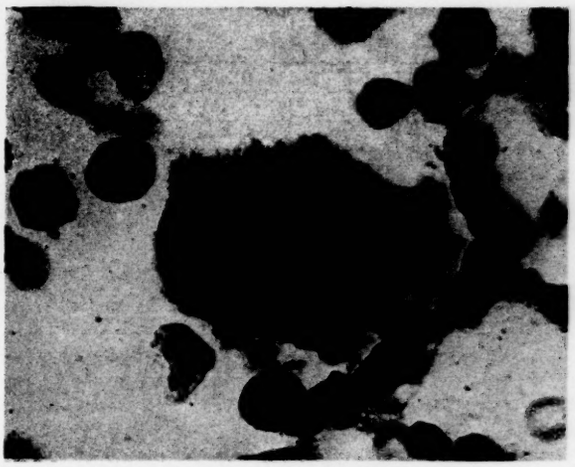


FIG. 3. A megakaryocyte as seen in the bone marrow two days after the intentionally produced reaction.

production, he concluded that an allergic process caused destruction of the platelets of the blood and inhibition of their production. Although the spleen undoubtedly plays an important role in the majority of the idiopathic cases, no evidence exists which would throw a light on its role in the allergic types unless the allergic reaction is mediated through the spleen.

Prothrombin Consumption. When blood is allowed to clot, the disappearance of prothrombin from the serum is proportional to the number of platelets provided that all other clotting factors are normal. Thus far this has been shown to be true of blood from normal subjects only when the number of platelets were varied artificially *in vitro*.[7] Figure 4 shows the prothrombin consumption curves obtained in our patient by plotting the prothrombin time of serum against time elapsed after firm clot had formed. It is evident that the slope of the curves increased as the patient's platelet count rose. Following the reaction produced by quinidine both the platelet count and prothrombin consumption dropped to almost zero and finally both returned to normal as the patient again recovered.

Although the prothrombin consumption curves thus paralleled the recovery of the patient and the rise in platelet count, they did not actually furnish a measure of the number of platelets present in the blood of the patient. Thus the platelet count ob-

tained on admission was slightly lower than that noted at the height of the intentionally produced reaction on the tenth hospital day; yet prothrombin consumption was significantly greater on entry than at the height of the reaction ten days later. Similarly pro-

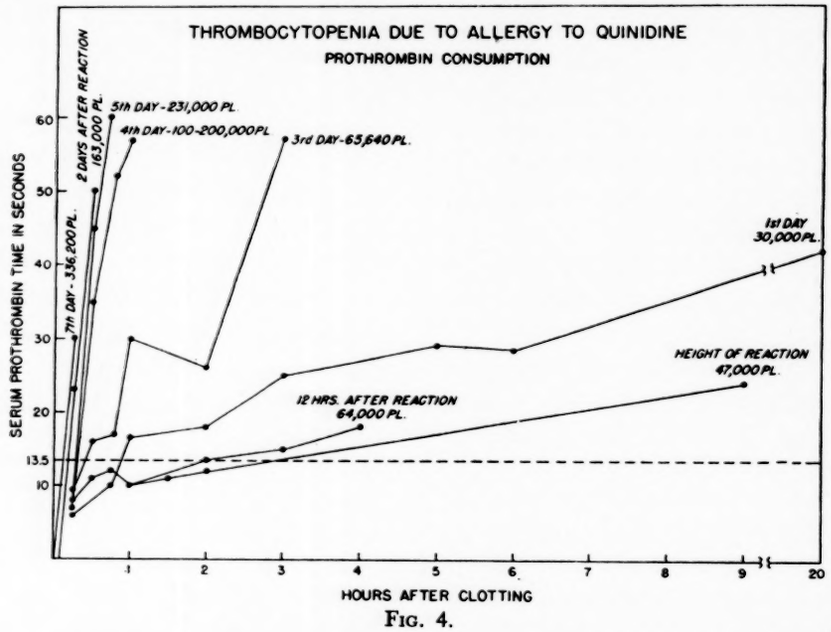


FIG. 4.

thrombin consumption was much greater on the third hospital day than on the tenth day, twelve hours after the reaction, even though platelet counts on these two occasions were practically identical. Further work will be necessary to explain this discrepancy.

Another interesting finding is the unusually low serum prothrombin time (under twelve seconds) when the platelet count was markedly reduced. In the light of present concepts this would indicate the presence of serum prothrombin accelerator substances or thrombin or both.

Diagnosis. On admission the chief finding suggesting an allergic process was a crusting deep purple hemorrhagic rash present around the patient's lips. It resembled eczema with hemorrhage into the lesions. Because of this picture and the lack of any previous bleeding tendency, the patient, her family and the referring physician were carefully questioned regarding contact with drugs and chemicals and only then was the intake of quinidine and its relationship to purpura brought to light. From our experience with previous cases in which apparently idiopathic thrombocytopenic purpura was accompanied with a skin reaction such as hives or another acute eruption we believe that the presence of a skin rash furnishes an important clue to the correct diagnosis, i.e., an allergic type of "idiopathic" thrombocytopenic purpura. The lack of eosinophilia both in the blood and bone marrow merely serves to remind one that allergic reactions are not necessarily accompanied with eosinophilia and that one should not be deceived by its absence.

Treatment. Spontaneous recovery began each time as soon as quinidine was withdrawn. There was thus no indication for splenectomy. The corollary to this statement is that the possibility of an allergic reaction should be carefully explored in every case of what appears to be idiopathic thrombocytopenic purpura, especially if splenectomy is contemplated.

SUMMARY

1. A case of "idiopathic" thrombocytopenic purpura due to hypersensitivity to quinidine is described.

2. The mechanism of the thrombocytopenia is discussed, emphasizing that in allergic thrombocytopenic purpura there may be not only inhibition of platelet formation but also a sudden increase in their destruction.

3. Diagnostically helpful features are mentioned and the occurrence of spontaneous recovery is emphasized.

REFERENCES

1. Beiglbock, W. Ein Fall von thrombopenischer Purpura bei echter Chininüberempfindlichkeit. *Ztschr. f. klin. Med.*, 131: 308, 1937.
2. Peshkin, M. M. and Miller, J. A. Quinine and ergot allergy and thrombocytopenic purpura. *J. A. M. A.*, 102: 737, 1934.
3. Brock, O. J. Thrombocytopenic purpura after administration of quinidine. *Nord. med.*, 10: 1542, 1941.
4. Nudelman, P. L., Leff, I. L. and Howe, C. O. Thrombopenic purpura following quinidine. *J. A. M. A.*, 137: 1219, 1948.
5. Soisalo, P. Thrombocytopenic purpura produced by quinidine. *Ann. med. int. Fenniae*, 36: 181, 1947.
6. Burstein, J. and Lamberg, B. A. Thrombocytopenia after quinidine medication; tetany and myocardial lesion. *Nord. med.*, 37: 473, 1948.
7. Quick, A. J., Shanberge, J. N. and Stefanini, M. The role of platelets in the coagulation of the blood. *Am. J. M. Sc.*, 217: 198, 1949.
8. Dameshek, W. and Miller, E. B. The megakaryocytes in idiopathic thrombocytopenic purpura, a form of hypersplenism. *Blood*, 1: 27, 1946.
9. Tocantins, L. M. The mammalian blood platelet in health and disease. *Medicine*, 17: 155, 1938.
10. Lawrence, J. S. and Valentine, W. N. The blood platelets: the rate of their utilization in the cat. *Blood*, 2: 40, 1947.
11. Hirsch, E. O., Favre-Gilly, J. and Dameshek, W. Thrombopathic thrombocytopenia; successful transfusion of blood platelets. *Blood*, 5: 568, 1950.
12. Moeschlin, S. Die Sedormid-Thrombozytopenie an hand von Sternalpunktaten, Belastungs-und Transfusionsversuchungen. *Schweiz. med. Wchnschr.*, 72: 119, 1942.

Book Review

Peptic Ulcer. A. C. Ivy, PH.D., M.D., J. Grossman, PH.D., M.D. and W. H. Bachrach, PH.D., M.D. 1,144 pages. Philadelphia, 1950. Blakiston Co. Cloth. *Price* $14.00.

This volume is a comprehensive and well written summary of present day knowledge of peptic ulcer. It will serve as a valuable reference work to the internist, the surgeon and to investigators in the field. The summaries at the close of each section of the book condense the extensive documented material with great clarity. The book is profusely illustrated and contains extensive bibliographies at the end of each chapter.

The authors have correlated existing knowledge of the cause, diagnosis and treatment of peptic ulcer. Part I deals with basic problems related to the healing of the stomach and duodenum, the resistance of the mucosa, the incidence of ulcer in lower animals and implantation of organs into the stomach.

Part II is devoted to the pathogenesis of ulcer. All of the important available experimental, autopsy and clinical observations relative to the subject are presented. In the chapter on the histophysiology of the acute ulcerative process the factors which may operate to impair the mucosa or interfere with healing are described. Chapters are devoted to the role of gastric and duodenal secretions in producing ulcer, the experimental production of ulcer, the role of the nervous system, constitutional factors and psychosomatic factors in etiology. Other chapters include a summary of information concerning the relation of intestinal and urinary extracts and a critical evaluation of the relation of nicotine, alcohol and caffeine to peptic ulcer. It is found that the conditions required for the formation of a peptic ulcerative defect can be stated rather precisely although the final cause of the disease remains unknown. Throughout the book the authors indicate the many aspects of the problem which require further study.

Part III deals with diagnosis. This section is a descriptive account of clinical patterns, laboratory and radiologic findings in the disease and its complications. The limitations of x-ray and gastroscopic methods in diagnosis are evaluated.

The final section is devoted to treatment. The massive literature on the results of medical treatment is well condensed and classified. The summaries of the results of various types of surgical therapy in ulcer and its complications will be of great value both to the internist and surgeon.

This volume represents a prodigious amount of work in assembling the world literature on ulcer.

C. A. F.

AUTHOR INDEX VOLUME IX

SUBJECT INDEX VOLUME IX

(E.) = Editorial

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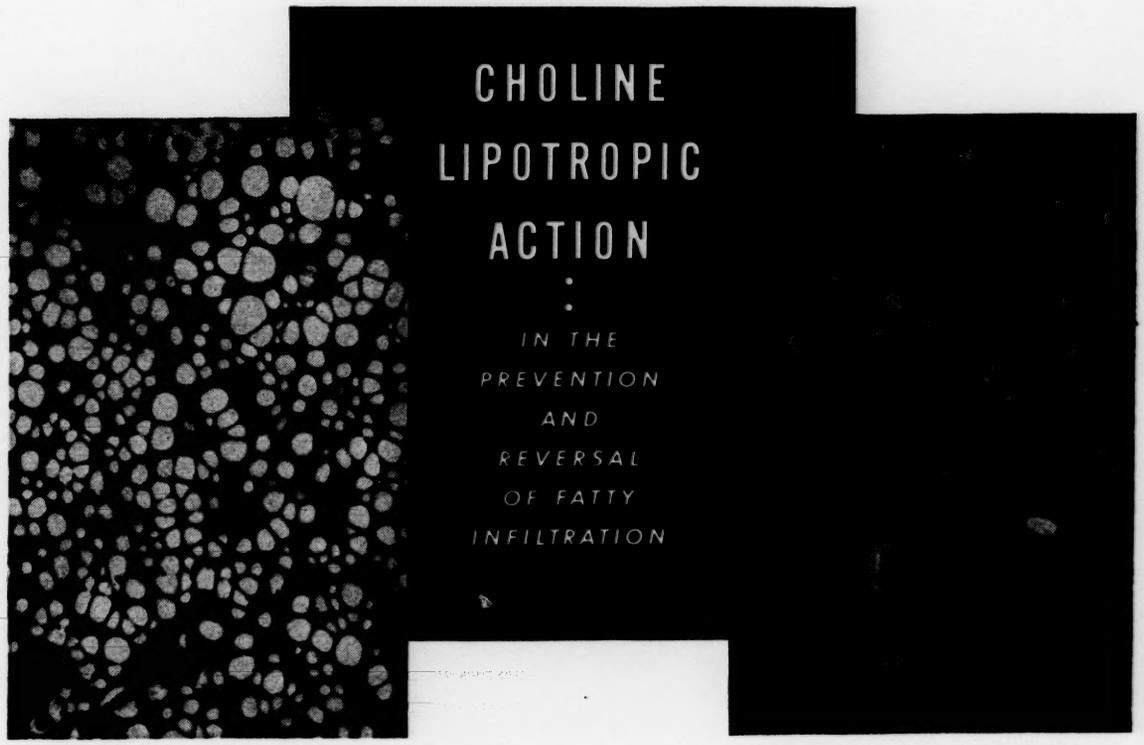
ORIGINAL ARTICLES



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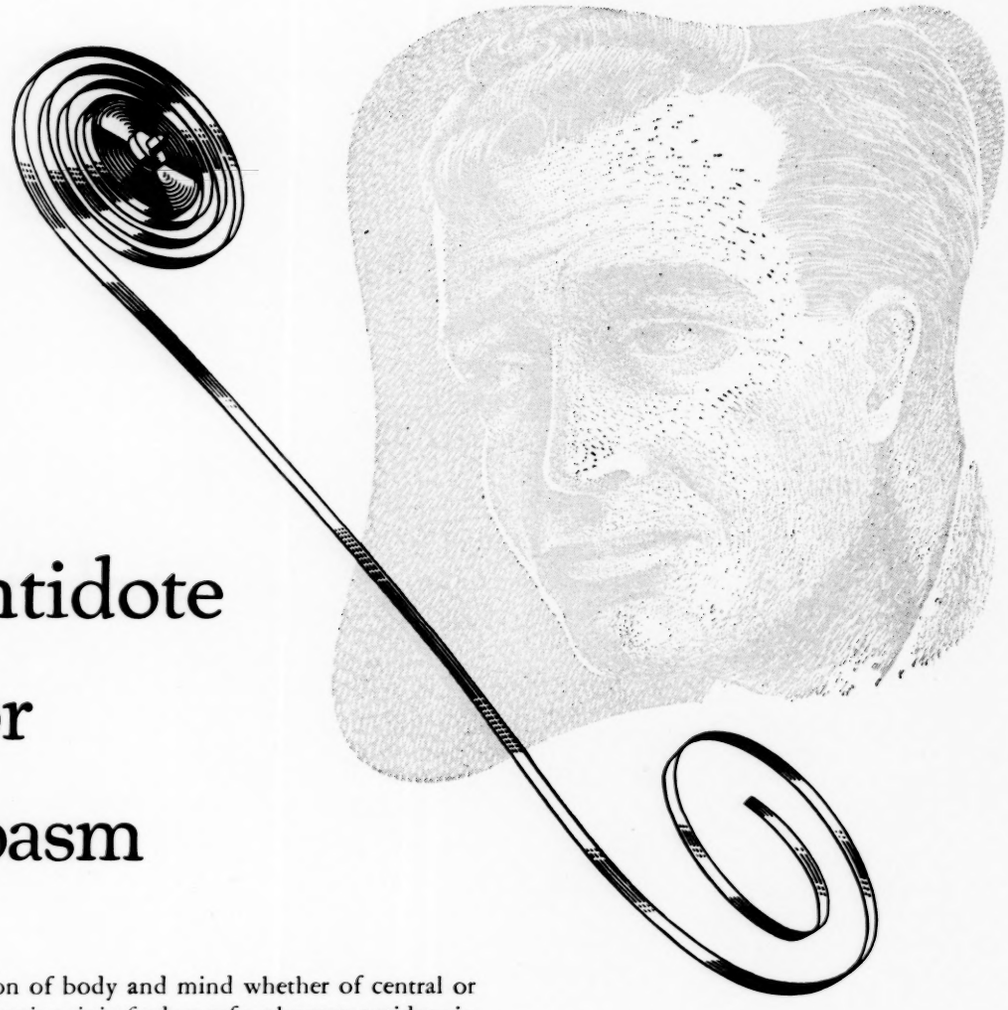

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1. Dieckmann, W. J., and Priddle, H. D.: Am. J. Obstet. & Gynec. 57:541, 1949.
2. Chesley, R. F., and Annitto, J. E.: Bull. Margaret Hague Mat. Hosp. 1:68, 1948.
3. Dieckmann, W. J., et al.: Am. J. Obstet. & Gynec. 59:442, 1950.
4. Kelly, H. T.: Pennsylvania M. J. 51:999, 1948.
5. Neary, E. R.: Am. J. Med. Sc. 212:76, 1946.

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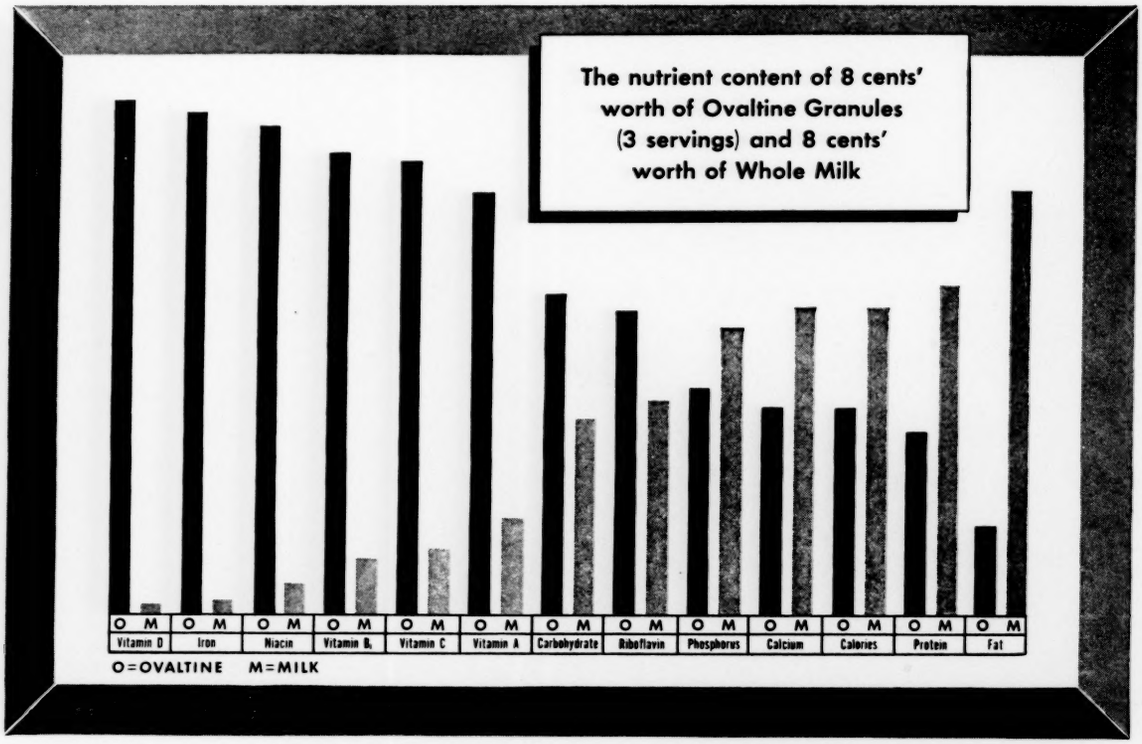

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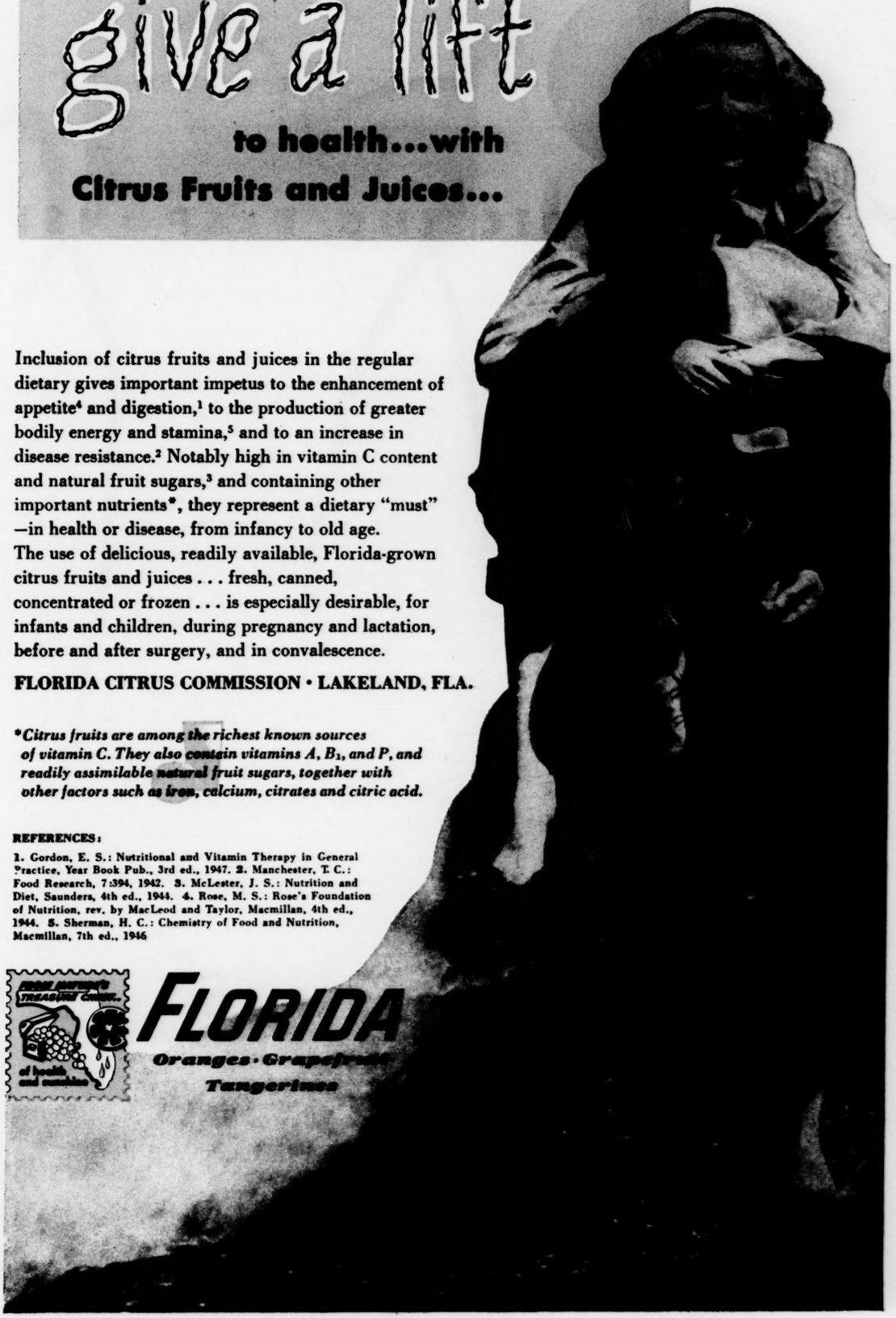


Inclusion of citrus fruits and juices in the regular dietary gives important impetus to the enhancement of appetite[4] and digestion,[1] to the production of greater bodily energy and stamina,[5] and to an increase in disease resistance.[2] Notably high in vitamin C content and natural fruit sugars,[3] and containing other important nutrients*, they represent a dietary "must" —in health or disease, from infancy to old age.

The use of delicious, readily available, Florida-grown citrus fruits and juices . . . fresh, canned, concentrated or frozen . . . is especially desirable, for infants and children, during pregnancy and lactation, before and after surgery, and in convalescence.

FLORIDA CITRUS COMMISSION • LAKELAND, FLA.

****Citrus fruits are among the richest known sources of vitamin C. They also contain vitamins A, B_1, and P, and readily assimilable natural fruit sugars, together with other factors such as iron, calcium, citrates and citric acid.***

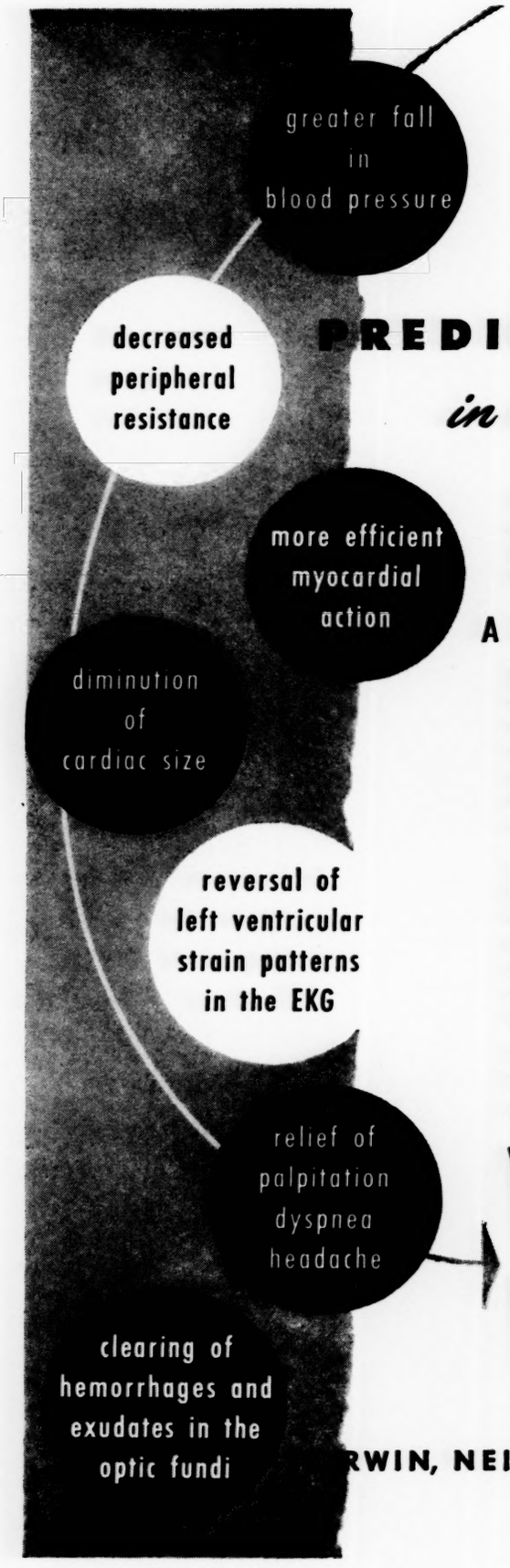
REFERENCES:

1. Gordon, E. S.: Nutritional and Vitamin Therapy in General Practice, Year Book Pub., 3rd ed., 1947. 2. Manchester, T. C.: Food Research, 7:394, 1942. 3. McLester, J. S.: Nutrition and Diet, Saunders, 4th ed., 1944. 4. Rose, M. S.: Rose's Foundation of Nutrition, rev. by MacLeod and Taylor, Macmillan, 4th ed., 1944. 5. Sherman, H. C.: Chemistry of Food and Nutrition, Macmillan, 7th ed., 1946

FLORIDA

Oranges · Grapefruit

Tangerines



PREDICTING RESPONSE
in essential hypertension

Striking objective improvement, in the individual case, can be obtained with veratrum viride Biologically Standardized in Craw Units, as available in VERATRITE and VERTAVIS.

A Therapeutic Alternative

In mild and moderate hypertension (Grades I and II), which accounts for more than 70 per cent of all hypertensive cases, VERATRITE is the choice of therapy and may be used routinely in everyday practice without undesirable side-effects. VERATRITE contains, in each tabule, veratrum viride (3 Craw Units) with sodium nitrite and phenobarbital.

In severe, resistant hypertension (Grade III) *and hypertension complicated by cardiac failure,* VERTAVIS can effect dramatic response. Adequate supervision of the patient and fine adjustment of dosage to the individual case are essential. VERTAVIS is a single agent, containing in each tablet veratrum viride (10 Craw Units).

Samples and literature on both VERATRITE and VERTAVIS, including clinical reports, are available on request.

Veratrite®
for mild and moderate hypertension

Vertavis®
for severe, resistant hypertension

RWIN, NEISLER & CO. • DECATUR, ILLINOIS

COME AND GET IT!

A new formula

for nourishment!

Delicious!

Concentrated!

Delmor®

nutrient powder

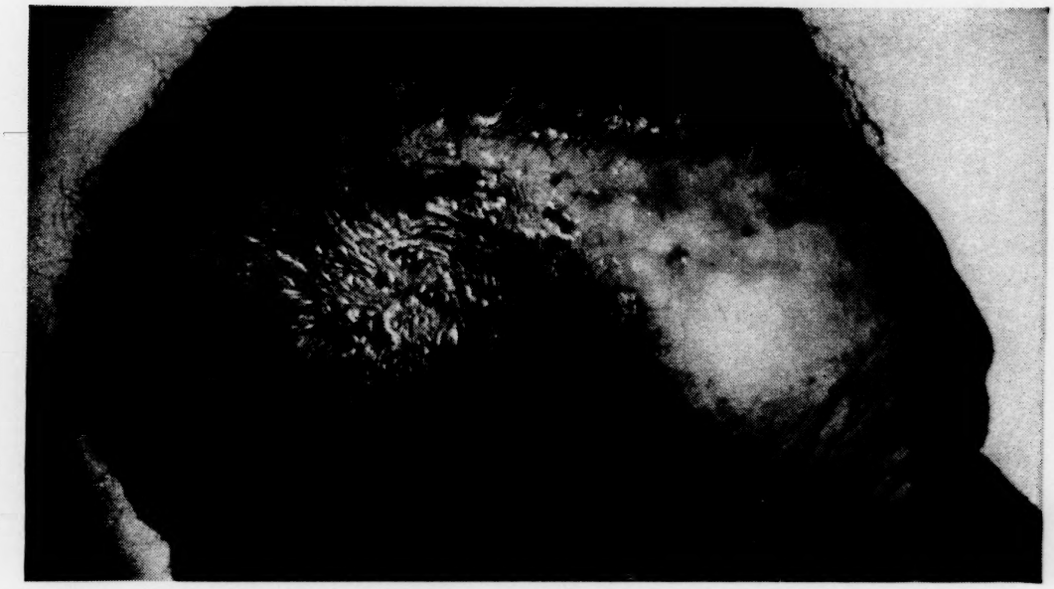
SHARP & DOHME

Each 100 Gm. of DELMOR® contains:

PROTEIN	(N x 6.25) derived from milk and soybean . . . . 50 Gm.
CARBOHYDRATE	derived from cane, milk and grain sugars and soybean 20 Gm.
MINERALS	Calcium . . . . . 600 mg. Phosphorus . . . . . 440 mg. Iron . . . . . 15 mg.
VITAMINS	Thiamine HCl (vitamin B_1) . . . . . 10 mg. Riboflavin (vitamin B_2) . . . . . 10 mg. Pyridoxine HCl (vitamin B_6) . . . . . 1 mg. Calcium pantothenate . . . . . 5 mg. Niacinamide . . . . . 100 mg. Ascorbic acid (vitamin C) . . . . . 100 mg. Vitamin A . . . . . 4,000 U.S.P. units Vitamin D . . . . . 400 U.S.P. units
LIVER	Whole liver substance, together with other natura factors of the vitamin B complex, including vitamin B_{12} 1 Gm.

DELMOR is a new and exceptionally useful formula for supplementing presurgical, obstetric, or convalescent diets with highest quality whole protein and other essential nutrients. A deliciously flavored powder, DELMOR may be given cooked or uncooked, with any kind of food, or between meals. Supplied in 1-lb. and 5-lb. bottles. Literature and recipes on request. Sharp & Dohme, Philadelphia 1, Pa.

Preferred therapy **in scalp disorders**



In the control of dandruff and in the general care of the seborrheic scalp, few preparations have proved as effective as Pragmatar—the outstanding tar-sulfur-salicylic acid ointment.

Pragmatar is also valuable in infants' "cradle cap"; in eczematous eruptions of the scalp, particularly those with a seborrheic component; and in seborrheic psoriasis of the scalp.

Pragmatar's superior oil-in-water emulsion base was specially developed for use on hairy surfaces. Pragmatar is non-gummy and non-staining; easy to apply and easy to remove.

PRAGMATAR

Highly effective in an unusually wide range of common skin disorders

Smith, Kline & French Laboratories, Philadelphia

'Pragmatar' T.M. Reg. U.S. Pat. Off.

emphasis on dosage

Clinical experience with vitamin E therapy indicates that its full metabolic effect is secured only with adequate, prolonged dosage.

"One of the most striking observations is the delay before the patient begins to notice improvement."

A. H. Ratcliffe: Lancet 2:1128 (Dec. 17) 1949.

ESORB*

VITAMIN E PREPARATION, WYETH

provides the optimum benefits of vitamin E therapy because it features:

- High potency;
- Ready absorption, assured by a solubilizing agent;
- Patient-acceptance, because of ease of administration.

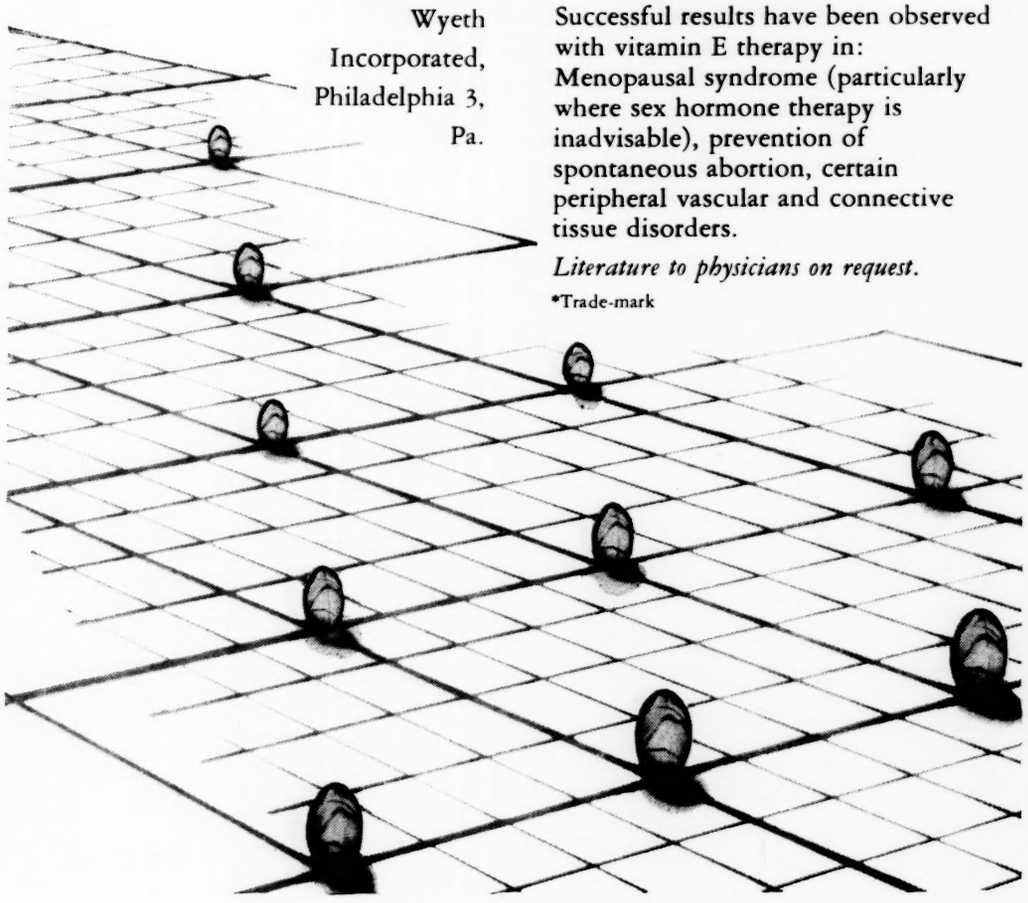
Successful results have been observed with vitamin E therapy in: Menopausal syndrome (particularly where sex hormone therapy is inadvisable), prevention of spontaneous abortion, certain peripheral vascular and connective tissue disorders.

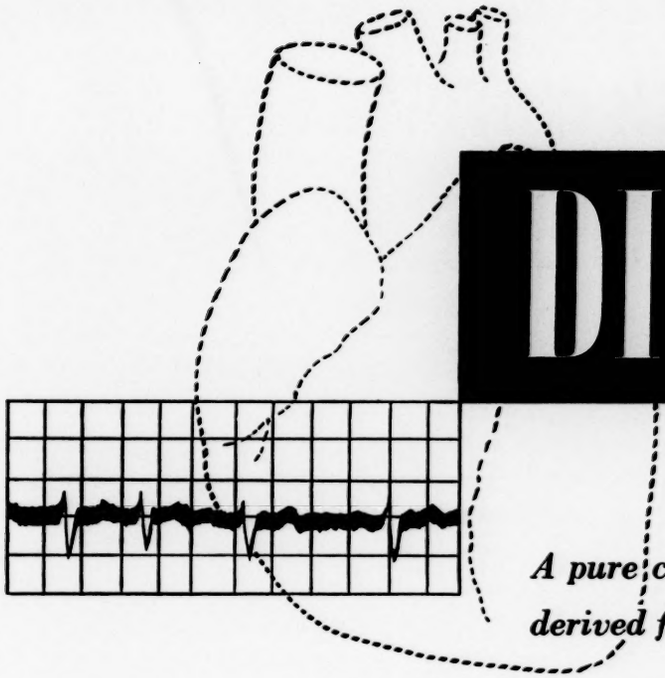
Literature to physicians on request.

*Trade-mark

Wyeth®

Wyeth Incorporated, Philadelphia 3, Pa.





DIGOXIN

'B.W.&Co.'

A pure crystalline glycoside derived from Digitalis lanata

Digoxin has been selected for use in fundamental studies on the hemodynamics of heart failure[1] and as a glycoside of choice for practical clinical treatment of heart failure[2] and auricular flutter.[3]

Harvey et al.[1] stated that in patients with left-sided heart failure "Digoxin produced a significant rise in cardiac output and stroke volume accompanied by a decrease in pulmonary arterial pressure."

Schaaf et al.[3] have concluded from their studies at the Massachusetts General Hospital that in the treatment of auricular flutter "digoxin was preferred to digitoxin or digitalis for this purpose because of its greater margin of safety."

1. Harvey, R.M.; Ferrer, M.I.; Cathcart, R.T.; Richards, D.W., and Cournand, A.: Some Effects of Digoxin upon the Heart and Circulation in Man: Am. J. Med. 7:439 (Oct.) 1949.

2. Batterman, R.G., and DeGraff, A.C,: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin, and Lanatoside C, for the Management of Ambulatory Patients with Congestive Heart Failure: Am. Heart J. 34:663 (Nov.)1947.

3. Schaaf, R.S.; Hurst, J.W., and Williams, C.: The Management of Auricular Flutter: Med. Clin. N. Am. p. 1255 (Sept.) 1949.

BURROUGHS WELLCOME & CO. (U.S.A.) INC.

TUCKAHOE 7, NEW YORK

NOW, peak performance in non-narcotic COUGH CONTROL with ROBITUSSIN®

'ROBINS'

In Robitussin, Robins now makes available a potent new and different therapeutic weapon for the relief of cough. Its major component is glyceryl guaiacolate, shown by recent dependable investigative techniques to be unexcelled for its intense and prolonged action in increasing R.T.F. (respiratory tract fluid).[1,2,3] Also included in the Robitussin formulation is desoxyephedrine—an adrenergic agent to prevent bronchial spasm[5]—which lifts mood and improves patient's sense of well-being.[4] Robitussin's highly palatable aromatic syrup vehicle appeals to young and old alike. Robitussin makes expectoration easier and freer and diminishes dry, irritating cough. It is non-toxic, non-narcotic.

USES: Acute colds of head and chest, bronchitis, laryngitis, tracheitis, pharyngitis, pertussis, influenza and measles. Helpful as a palliative of harmful cough in tuberculosis, asthma and paranasal sinusitis.

FORMULA: Each 5 cc. (1 teaspoonful) of Robitussin contains:

Glyceryl guaiacolate	100 mg.
Desoxyephedrine hydrochloride	1 mg.

In a palatable aromatic syrup

DOSAGE: Adults: 1 to 2 teaspoonfuls, repeated every 2 to 3 hours as necessary. Children: ½ to 1 teaspoonful according to age, 3 or more times daily.

SUPPLIED: In pints and gallons.

REFERENCES

1. Boyd, E. M. et al.: Canadian J. Res., 23:195, 1945.
2. Boyd, E. M. et al.: Canadian M.A.J., 54:216, 1946.
3. Connell, W. F. et al.: Canadian M.A.J., 42:220, 1940.
4. Foltz, E. E. et al.: J. Lab. & Clin. Med., 28:603, 1943.
5. Novelli, A. and Tainter, M. L.: J. Pharmacol., 77:324, 1943.

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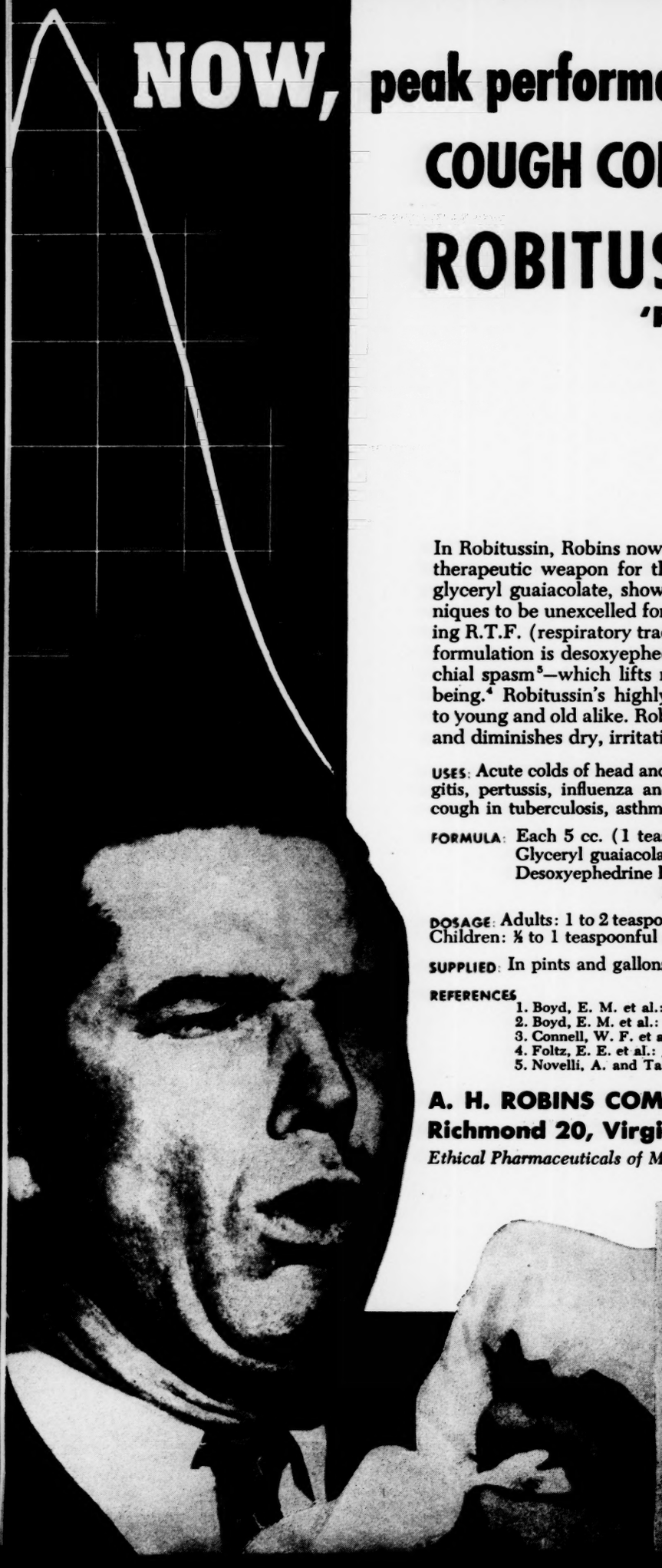

to facilitate productive cough . . .
to minimize harmful cough

℞ Robitussin

Robins